JPRS-JST-86-011

21 APRIL 1986

Japan Report

SCIENCE AND TECHNOLOGY

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JAPAN REPORT

SCIENCE AND TECHNOLOGY

CONTENTS

BIOTECHNOLOGY

DEVELOPMENT OF SLOW-RELEASE HORMONE CARRIERS

Tokyo BIO INDUSTRY in Japanese Dec 85 pp 18-28

[Article by Hidishi Yamanaka, Professor of Urology, Faculty of Medicine, Gumma University]

[Original abstract] Our group has been engaged in researching slow-releasing hormone carriers. At present, we have reached the stage of clinical applications of (1) artificial testes to release testosterone, and (2) compounds of high molecular carriers and LH-RH agonists. This article discusses basic and clinical data on these two cases.

[Text] 1. Introduction

It is possible to slowly release drugs by compounding medicines with carriers such as high [molecular weight] molecules. Drugs that have short half lives in blood and whose concentrations cannot be easily maintained at physiologically effective levels for a long period or drugs that work best when they act slowly and in minute quantities are far more effective by releasing them slowly. In addition, by slowly releasing these drugs, their side effects are reduced, and even methods for administering such drugs can be improved. For several years now, we have been studying hormones because we recognize that "hormones will work best when slowly released." In this article, we will discuss slow-releasing hormone carriers, focusing our attention on two studies (of slow-releasing testosterone and LH-RH agonists) that reached the clinical application stages.

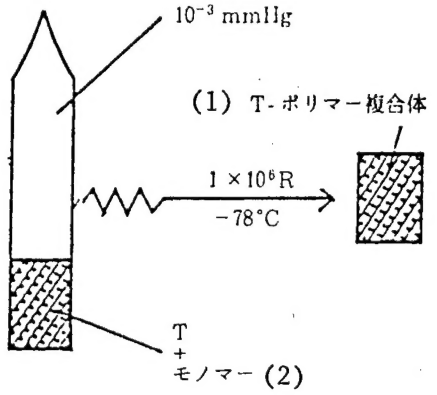
2. Compounds of Testosterone and Nonbiodegradable High Molecular Carriers

2.1 Fabrication method

The method used to fabricate a compound of testosterone and a nonbiodegradable high molecular carrier is shown in Figure 1. As a high molecular carrier, a vitrifiable monomer, which does not crystallize easily at low temperatures but easily reaches a stable, low-temperature, supercooled state, was used to convert drugs into plastic polymers by radiation-induced polymerization in low-temperature, supercooled states.[1-3] Testosterone was added to the monomer or comonomers mixed in an appropriate ratio. This mixture was injected into a glass casting ampule, the ampule was sealed, and the pressure inside the

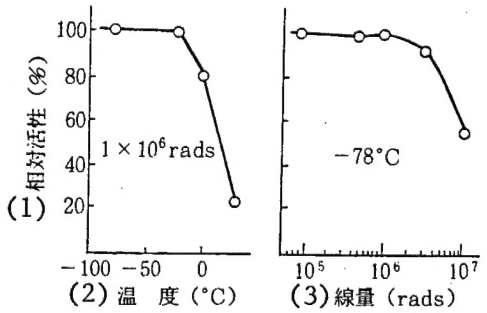
ampule was kept at 10^{-3} mmHg. The ampule was then irradiated by gamma rays from a ^{60}Co source with a dose of 10^6 rads while its temperature was kept at -78°C. The compound of the hormone and the high polymer carrier was fabricated by thus polymerizing the monomer. This radiation-induced polymerization has the advantages that it does not introduce any catalysts into the compound since the method does not use catalysis, it forms compounds without losing any physiological activity even for physiologically active materials that are unstable against heat, and deep inside, the compound is sterilized because it has been irradiated at a high radiation dose rate.

Figure 1. Fabrication of a compound of testosterone and a nonbiodegradable, high molecular carrier.



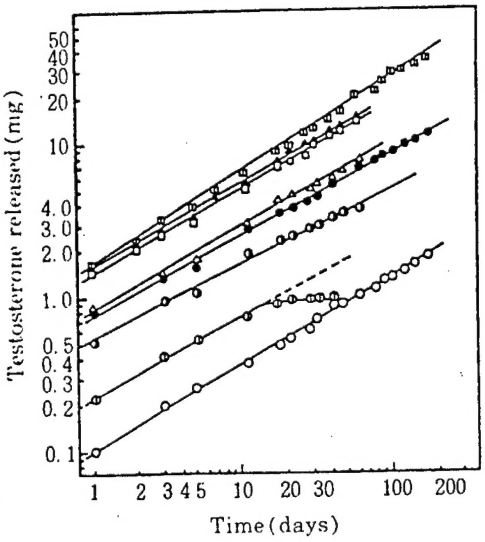
Key to Figure 1:
1. Testosterone-polymer compound 2. Monomer
T: Testosterone
Testosterone and a high molecular monomer are injected into a glass casting ampule and irradiated by gamma rays (10^6 rads) at -78°C and 10^{-3} mmHg to polymerize the monomer and fabricate a testosterone high-polymer compound.

Figure 2.[2] Study of testosterone stability against temperature and irradiation.



Key to Figure 2:
1. Relative activity 2. Temperature
3. Radiation dose

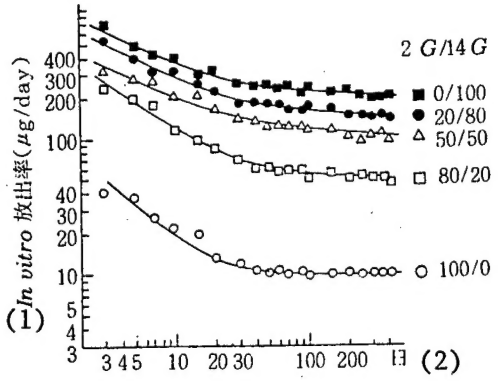
Figure 3.[5] Release of testosterone from various compounds of testosterone and polymers.



Key to Figure 3:
Hydrophilicities of these polymers are ranked as 2G < NPG < GMA < TMPT < 4G < HEMA < 9G < 14G. Testosterone release rates are correlated to the hydrophilicities of these compound polymers.

(○) Diethylene glycol dimethacrylate(2G)
(◫) Neopentyl glycol dimethacrylate (NPG)
(◑) Glycidyl methacrylate(GMA)
(●) Trimethylolpropane trimethacrylate (TMPT)
(△) Polyethylene glycol #200 dimethacrylate (4G)
(□) 2-hydroxyethyl methacrylate (HEMA)
(▲) Polyethylene glycol #400 dimethacrylate (9G)
(▥) Polyethylene glycol #600 dimethacrylate (14G)

Figure 4.[3] Examination of in vitro testosterone release rate from a copolymer (2G/14G).



Key to Figure 4:

1. In vitro release rate 2. Days

This examination of testosterone release rates from a copolymer carrier formed by mixing polyethylene glycol #600 dimethacrylate (14G), a hydrophilic vinyl polymer, and diethylene glycol dimethacrylate (2G), which is a hydrophobic vinyl polymer, was carried out using the TR-5S elution testing device manufactured by Tomiyama Industries. We found that testosterone release rates changed when the composition ratio of 2G and 14G was changed.

Table 1. Variations of prostate weight and serum hormones (short term) after implanting a compound of testosterone and a polymer.[6]

	(1)体重 (g) (2)前	(3)後	(4)前立腺腹葉 (mg/100g·B.W.)	血清テストステロン (5) (ng/mℓ)	血清LH (6) (ng×Sl/mℓ)	血清FSH (7) (μg×Sl/mℓ)
2 週 (8) (4)	356.00 ± 3.34	420.00 ± 14.29	89.38 ± [illegible]**	4.23 ± 0.41**	0.163 ± 0.04**	0.818 ± 0.04**
4 週 (9) (5)	359.00 ± 1.42	470.00 ± 11.68	10[illegible].70 ± 2.51**	n.d[1)]	0.409 ± 0.07**	0.897 ± 0.04**
8 週 (10) (5)	335.00 ± 0.92	464.00 ± 3.66	107.34 ± 1.03**	3.25 ± 0.24**	0.285 ± 0.04**	1.077 ± 0.06**
去勢コントロール (11) (5)	351.00 ± 1.19	474.00 ± 4.66	4.32 ± 0.04	0.36 ± 0.02	12.270 ± 0.65	2.466 ± 0.05

(12)テストステロン・ポリマー複合体を2個ずつ去勢雄 Wistar 系ラット背部皮下に移植し，前立腺重量，血清テストステロン，血清 LH, FSH ，を移植後2，4，8週に測定した。

n.d[1)]：not determined.

** ：P＜0.001 （コントロールに対して）(13)

Key to Table 1:

1. Body weight
2. Before
3. After
4. Ventral prostate
5. Serum testosterone
6. Serum LH
7. Serum FSH
8. 2 weeks [later]
9. 4 weeks
10. 8 weeks
11. Castrated control
12. Two pellets of testosterone-polymer compounds were implanted under the dorsal skin of eunuch Wister rats. Their prostate weights, serum testosterone, serum LH, and [serum] FSH were measured 2, 4, and 8 weeks after the implantation.
13. (Compared to the control rats)

Table 2. Prostate weights and amount of serum hormones in eunuch rats one year after testosterone-polymer compounds were implanted.

(1)移植複合体数	ラット数 (2)	体重 (3)(g)	(4)前立腺腹葉 (mg/100g. B.W.)	(5)血清 LH (ng×Sl/mℓ)	(6)血清 FSH (μg×Sl/mℓ)	血清テストステロン (ng/mℓ)(7)
0	5	492 ± 4	4.43 ± 0.10	4.642 ± 0.208	3.621 ± 0.258	≤ 0.20
2	2	560 ± 7	68.83 ± 4.48**	0.875 ± 0.036**	1.642 ± 0.094**	0.48 ± 0.001**
3	2	565 ± 11	96.29 ± 3.77**	0.109 ± 0.010**	0.888 ± 0.017**	0.61 ± 0.07**

** : P< 0.001 (コントロールに対して) (8)

Key to Table 2:
1. Number of implanted compound [pellets]
2. Number of rats
3. Body weight
4. Ventral prostate
5. Serum LH
6. Serum FSH
7. Serum testosterone
8. (Compared to control rats)

2.2 Release of testosterone from a nonbiodegradable, high molecular carrier compound

Some drugs lose their physiological activity according to temperature and radiation dose. Hence, in fabricating compounds of testosterone and high molecular carriers, one must examine how irradiation doses and temperatures will affect the testosterone itself. Results of such studies are presented in Figure 2. With a dose of 10^6 rads, it has been confirmed that testosterone is stable at the temperature ranges of -20°C to -100°C. With a dose range of 10^5 to 10^6 rads, testosterone is stable at -78°C. With this knowledge, we proceeded to examine the in vitro eluting behavior of testosterone after a compound of testosterone and a high molecular carrier was formed by radiation induced polymerization. In general, it has been pointed out that the hydrophilicity of the carrier itself is an important factor, affecting the release of medicine by a compound of a drug and a vinyl high molecular carrier. This is also the case for testosterone; the release rate of testosterone from a compound increases (Figure 3) as more hydrophilic polymers are used as carriers. When a mixture of polymers with different hydrophilicities is used as a carrier, the testosterone release rate depends on the mixing ratio. For instance, Figure 4 shows testosterone release rates from compounds with copolymer carriers fabricated by mixing a hydrophilic vinyl polymer, polyethylene glycol #600 dimethacrylate (14G), with a hydrophobic vinyl polymer, diethylene glycol dimethacrylate (2G). The figure clearly shows that the release rates depend on the composition ratio of the two polymers. When two kinds of polymers are mixed, the release rate of testosterone from a compound of vinyl polymer carriers can be controlled by changing the polymer composition ratios. Thus, we studied in vivo release from various vinyl polymer carrier compounds, from which the release of testosterone had been confirmed through in vitro elution tests (Table 1). We transplanted two pellets of a compound of testosterone and a vinyl polymer

carrier (each pellet contained 150 mg of testosterone with an initial release rate of 100 μg per day, [the carrier consisted of] polystylene/diethylene glycol dimethacrylate [in the ratio] (10/90), and the pellets were disks 80 mm in diameter and 6 mm thick) under the dorsal skin of castrated Wister male rats, Then, the prostate weight and the values of serum testosterone, LH, and FSH were measured 2, 4, and 8 weeks after implantation. After two weeks, both serum LH and FSH values declined significantly, while the level of serum testosterone remained at 3-4 ng/mℓ throughout the testing period. The prostates that had shrunk because of castration returned to their normal size after four weeks. Then, we implanted two and three pellets of the same type of testosterone-vinyl polymer carrier compound, sacrificed the rats after one year, and measured the prostate weights and the levels of serum testosterone, LH, and FSH (Table 2). Although the measured levels of serum testosterone were 0.48 ng/mℓ when two pellets were implanted and 0.61 ng/mℓ when three pellets were implanted, both values being well below 1 ng/mℓ, the levels of [serum] LH and FSH were well under control because testosterone had been released slowly over an extended period. The prostate weight was also normal when three pellets were implanted, 96.29 mg/100 g B.W. These results indicate that testosterone has been released throughout the long period of one year and continued to act physiologically.

2.3 Clinical applications of testosterone-high molecular carrier compounds--Artificial testes with testosterone releasing capability

In addition to producing sperm, testes generate and secrete male hormones. The main male hormone secreted by testes is testosterone. Serum testosterone of a normally developing male increases as he enters puberty, his genitals and accessory sex organs develop, and secondary sex characteristics appear. However, if no testosterone is secreted from his testes during this period, secondary sex characteristics cannot be observed. Since such a person exhibits symptoms similar to eunuchs, this is called eunuchoidism. Also, if an adult male loses both testes because of an accident or malignant tumors of testes, his genitals and accessory sex organs will atrophy and become impotent, and he will experience psychological and character changes. Patients with eunuchoidism and those who lost both testes by accidents or malignant tumors require treatment to supplement testosterone. In the past, injections of testosterone depots were used as treatment to supplement testosterone. This injection treatment, however, has several defects. One of these defects is that frequent visits to the doctor are necessary because the sustaining effect of one injection, though of the depot type, is short, lasting only 2-3 weeks. Eventually the patient stops visiting the doctor's office. Moreover, serum testosterone concentration right after an injection is unnecessarily high. Another defect is that the patient's complex that he "does not have any testes" cannot be overcome by this injection treatment. Artificial testes have been inserted into the patients who lost testes by operations or accidents,. The artificial testes used so far are only for cosmetic formation; they do not secrete any male hormones. The artificial testes we have developed not only satisfy cosmetic objectives but also perform the function of releasing testosterone. Based on the test results of in vitro release [of the hormone], we implanted artificial testes in the backs of castrated rabbits and confirmed that testosterone is slowly but continuously

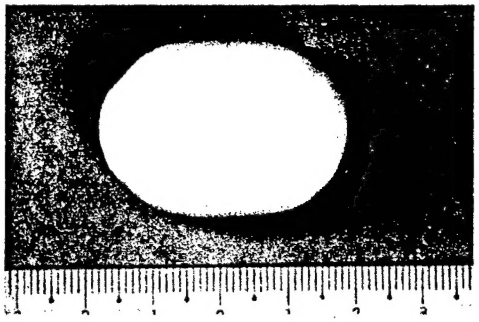
released for a long period of tens of weeks.[7,8] Encouraged by these animal test results, we decided to begin clinical applications of the artificial testosterone releasing testes. We explained to a few eligible patients that these artificial testes are being used in clinical tests for the first time, received their consent, and then inserted the artificial testes in their scrota. The test-fabricated artificial testis is egg shaped (35 mm x 25 mm) and contains 6-7 grams of testosterone (Figure 5). In Table 3, we present the time variations of serum testosterone, LH, and FSH after inserting artificial testes into two of the eunuchoidism patients who were tested. In both clinical cases, one artificial testis was inserted in each side of the scrota.

Table 3. Time variations of serum testosterone, LF,[9] and FSH levels after inserting artificial testes that release testosterone.

Case		before	1 W	2 W	1 M	3 M	6 M	9 M
I. K., 29y	T (ng/mℓ)	0.7	6.4	9.4	4.8	8.6	4.8	4.4
(hypogonadotropic	LH(mIU/mℓ)	10.6	4.0	4.5	4.7	4.6	5.5	6.0
hypogonadism)	FSH(mIU/mℓ)	8.4	1.0	1.0	1.0	1.0	0.6	3.1
K. Y., 30y	T (ng/mℓ)	2.6	11.0	8.5	7.0	5.8	6.0	6.0
(hypergonadotropic	LH(mIU/mℓ)	74.3	59.2	n.d.	36.9	48.6	62.3	66.3
hypogonadism)	FSH(mIU/mℓ)	54.9	39.0	n.d.	28.8	37.5	46.1	51.9

n.d. : not determined

Figure 5. Testosterone releasing artificial testis.



One week after the insertion, we detected 6.4 ng/mℓ of serum testosterone in clinical case I.K. and 11.0 ng/mℓ in clinical case K.Y. Thereafter, the levels of serum testosterone in both clinical cases decreased relatively slowly. Even after 9 months, serum testosterone levels remained normal, 4.4 ng/mℓ for clinical case I.K. and 6.0 ng/mℓ for clinical case K.Y. In both cases, serum gonadotrophin levels decreased one week after the insertion of artificial testes and remained low. After a few months, however, the levels tended to return to those before the implantation. In the clinical case I.K., to whom an androgen supplementing treatment was applied for the first time, the drug's clinical effects were conspicuous; his pubic hair and beard grew, his penis enlarged, and other male characteristics, such as voice alteration, changed a few weeks after the insertion of the artificial testes. After 9

months, his bone frame, appearance, and character became masculine. The test-fabricated and clinically used artificial testes contained 6-7 grams of testosterone. They were designed to release a few mg of the hormone per day, and hence theoretically testosterone would be released continuously for 4-5 years. Ideally, a steady, long-term effect is desirable, as well as artificial testes that use materials with a hardness closer to the real testes. These points should be improved in the future.

3. Nonbiodegradable Compounds of LH-RH Agonist High Polymer Carriers

3.1 Fabrication method

In contrast to drugs that do not dissolve in water well, such as testosterone, water soluble drugs cannot be made into simple, uniform compounds with high molecular [weight] monomers that release slowly for a long period. Since LH-RH agonists are water soluble, we must find a special method to make them release slowly. In Figure 7, a method to fabricate a compound of Leuprolide (also called TAP 144, see Figure 6), which is an LH-RH agonist, with polymer carriers is shown. Leuprolide powder was formed and processed into a hard pellet with a flat, round bottom under 400 kg/cm^2 pressure. To impede early elution from the compound, Whatman No. 1 filter papers were placed on the top and bottom of the processed Leuprolide pellet as fillers. The compound was formed by gamma-ray irradiation from a ^{60}Co source, after [the pressure vessel was] filled with high molecular vinyl monomers. The fabricated Leuprolide-high polymer carrier compound is 14 mm in diameter and 4 mm thick.

Figure 6. Chemical structure of Leuprolide [TAP 144, (D-Leu^6)-des Gly-NH_2^{10}-LHRH ethylamide].

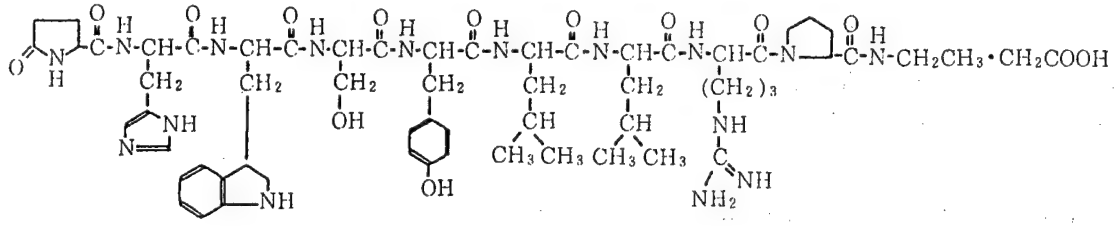
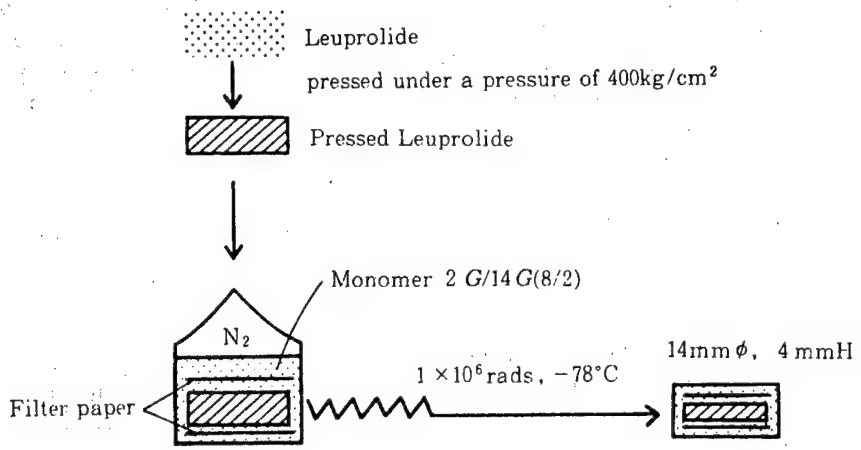


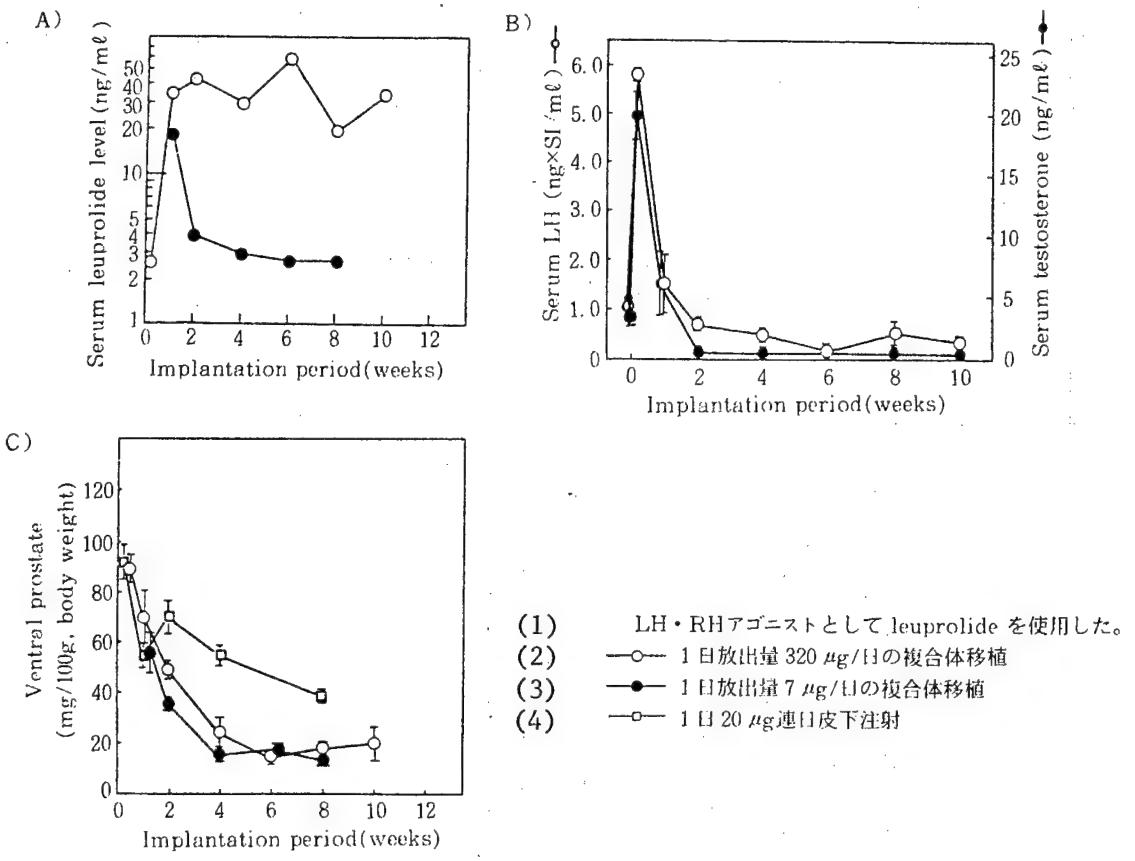
Figure 7. Fabrication of Leuprolide (TAP 144)-polymer compound.



3.2 Release of LH-RH agonists from a high molecular carrier compound that is nonbiodegradable

We found that, in the case of water soluble drugs such as LH-RH agonists, it was difficult to maintain zero order elution by simply changing the type of polymers combined or their mixing ratios. Hence, we tried using a sandwich structure with compounds of LH-RH agonists and polymers (see the section on fabrication method). As a result, we could maintain a [steady] zero order elution speed for an extended period by keeping a filler with the drug. In Figure 8, the prostate weight, levels of serum testosterone and LH, and concentration of LH-RH agonist (Leuprolide) are compared. In one case, compounds of LH-RH agonists and vinyl polymer carriers with a sandwich structure were implanted under the dorsal skin of male rats. The amounts of the compounds released daily were adjusted to 320 μg and 7 μg, respectively. These tests were compared to the values obtained after subcutaneous injections of 20 μg [of the same compounds] once a day. Serum Leuprolide concentration was maintained at a constant level for 10 weeks. Two weeks after the implantation and thereafter, the serum testosterone level was also maintained at the same level at the time of castration (see Figure 8 B). The prostate weight decreased. This effect was sufficiently conspicuous with a daily release of 7 μg. The compound that released [the hormone] slowly at a daily rate of 7 μg seems to have reduced the prostate weight much better than the daily subcutaneous injections of 20 μg. Our results indicate that biologically active LH-RH agonists were released over an extended period of 10 weeks from compounds of LH-RH agonists and vinyl polymers implanted under the skin.

Figure 8. Time variations of prostate weights and concentrations of serum LH-RH agonists, testosterone, and LH after compounds of LH-RH agonists and vinyl polymers were implanted under the dorsal skin of rats.



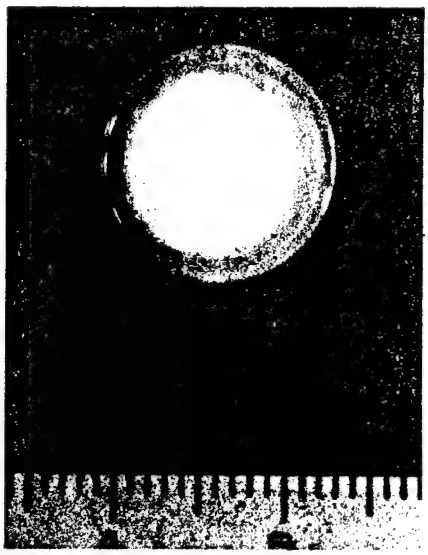
Key to Figure 8:
1. Leuprolide was used as the LH-RH agonist.
2. Implanted a compound with a daily release of 320 μg.
3. Implanted a compound with a daily release of 7 μg.
4. Daily subcutaneous injection of 20 μg.

3.3 Treatment of prostate cancers using compounds of LH-RH agonists and polymer carriers

About 80 to 90 percent of prostate cancers depend on androgens. For these androgen-dependent prostate cancers, antiandrogen treatments are widely used, estrogen treatments being the main ones. In Japan, we began to experience cases in which cardiovascular lesions occurred during estrogen treatments perhaps because of the westernization of our life style and eating habits. Thus, antiandrogen treatments with fewer side effects have been in great demand. This need was met with new drugs, RH-RH agonists. When a large dose of an LH-RH agonist is administered to a male animal, pituitary gland and testes functions are suppressed, and the concentration of serum testosterone is lowered to castrated levels. These "medical castration" effects act as

cancer inhibiting effects against prostate cancers. With these drugs, cardiovascular or liver lesions, which are observed occasionally when doses of synthetic estrogens are used, are not observed. Through several clinical studies, it has become clear that this agonist has cancer inhibiting effects equivalent to medialecital estrogen drugs.[10-12] However, before this drug is used to clinically treat prostate cancers, there is a point that must be clarified. It is the method of administering the drug. For the LH-RH agonist to be effective, a daily subcutaneous injection is necessary. Administering the drug through the nostrils is an alternative, but the absorption efficiency of the drug decreases. In order to be able to use this drug in actual clinical applications, it must be released slowly. In order to have the LH-RH agonist released slowly over an extended period, we fabricated a compound of the LH-RH agonist with a polymer (Figure 9). From the results of repeated animal experiments, the effectiveness and safety of the compound were confirmed.

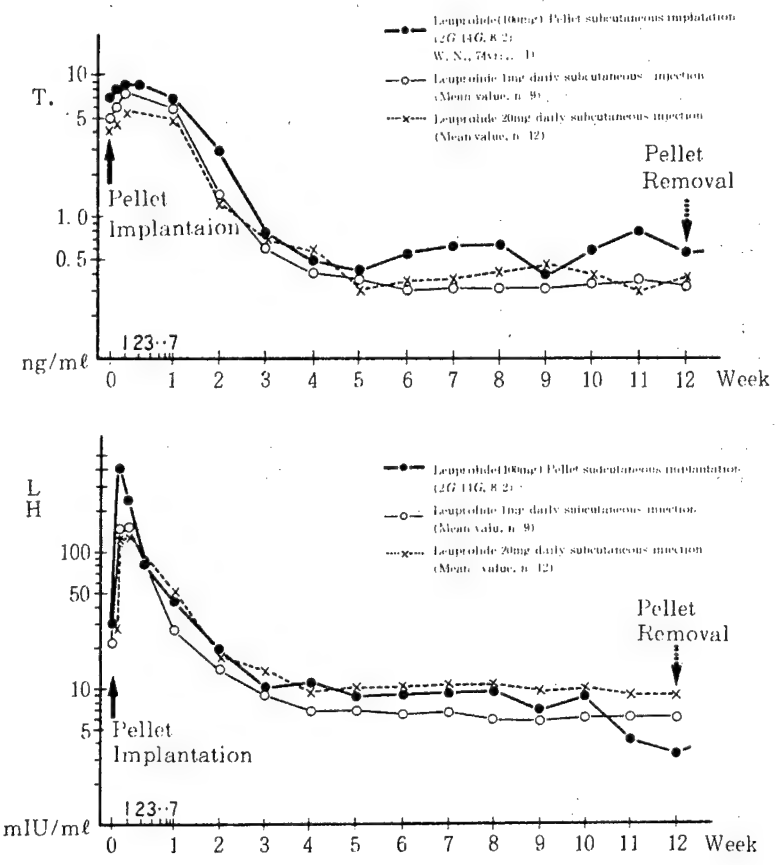
Figure 9. Compound of LH-RH agonist and high molecular carrier used in clinical studies.



Then, with the consent of a prostate cancer patient, the compound was implanted under his ventral skin. In Figure 10, we compare variations of serum LH and testosterone concentrations between a group of patients who took daily subcutaneous injections of 1 mg and 20 mg each and the patient who received a subcutaneous implantation of the Leuprolide (contains 100 mg)-vinyl polymer compound. Three weeks after the polymer compound implantation and thereafter, the patient's serum testosterone level went below 1 ng/mℓ, and his serum level remained at the castrated level throughout the 12-week study period, after which the compound was removed. His prostate cancer focus began to soften one month after implantation, atrophied after the 12-week period, and left only a partial hardening. There was also a notable improvement in his difficulties with urinating. According to a tissue examination conducted at the end of the 12-week period, a thin fibrous cover around the polymer

compound was formed (about 75 μm thick), but no inflammatory tissue reactions were observed. At present, more research is in progress, and a long-term, slow releasing capability that lasts longer than 6 months has been clinically confirmed.[13]

Figure 10. Time variations of serum testosterone and LH concentrations in a group of prostate cancer patients who received daily subcutaneous injections of Leuprolide in 1 mg and 20 mg doses and those of a patent in which a compound of Leuprolide and vinyl polymer carrier was implanted.



4. Compounds of LH-RH Agonists and Biodegradable, High Molecular Carriers

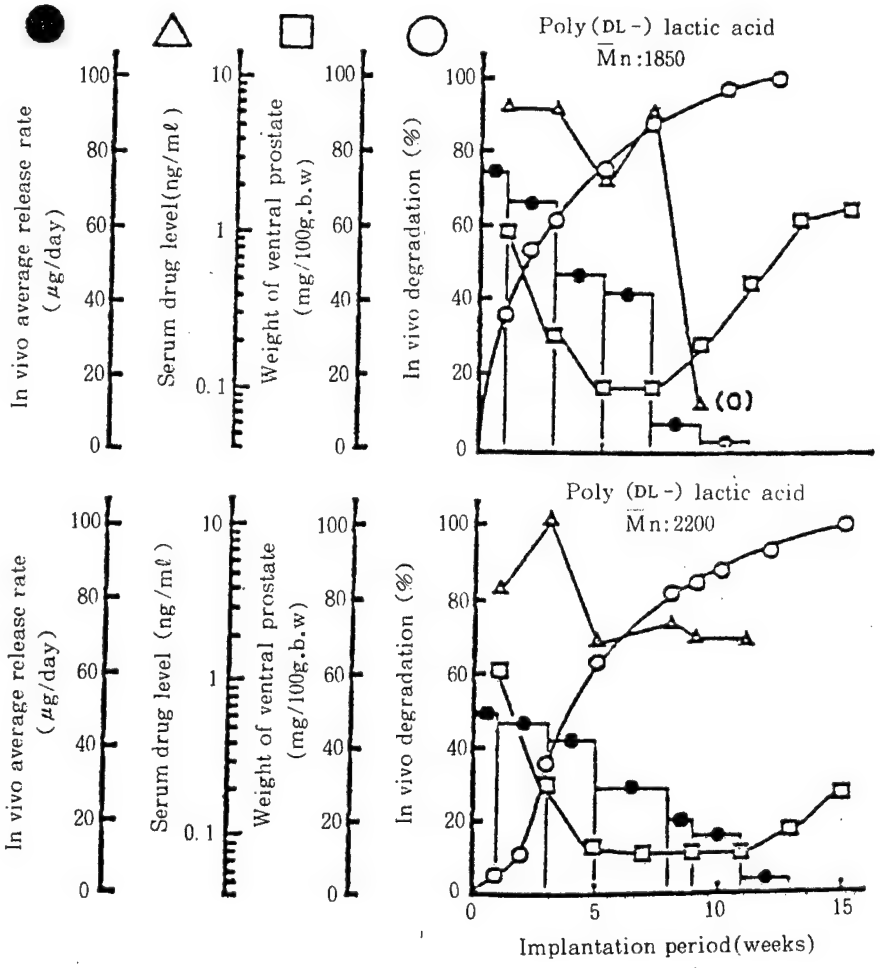
In the compounds described so far, high molecular carriers are not biodegraded and absorbed in vivo. Hence, the carriers must be removed from the body after the drugs have been released. When this slow release takes more than 3 months, one can tolerate nonbiodegradable carriers that will not be degraded at all in the body. It is more desirable, however, to use carriers that do not have to be removed, that is, carriers that will be degraded and absorbed into the body right after the drugs are released when a short-term, slow release within two months is required. We have developed a method to form a high density, high rigidity carrier by fusion processing polydipsipeptide, which consists of proteins, polyamino acids, polyoxyacids, amino acids, and oxyacids, under pressure and high temperatures without using any organic

solvents.[14,15] Among these carriers, we made sufficient progress in a carrier made from polylactic acid to use it for clinical studies.

4.1 Fabrication method and examination of drug's slow releasing capability

The poly(DL-)lactic acid was synthesized by dehydrating condensation. As the carrier, we used a poly(DL-)lactic acid with an average molecular weight of 1850 and another with an average molecular weight of 2200. The former exhibited hyperbolic biodegradation and the latter S-shaped biodegradation.

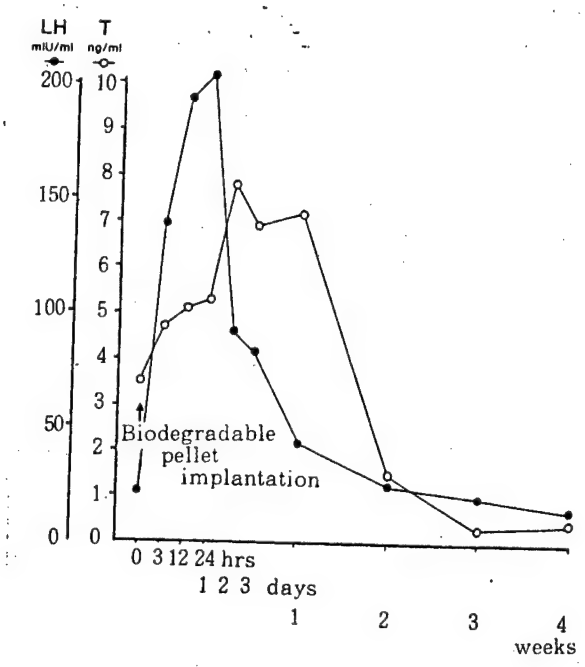
Figure 11. Time variations of Leuprolide elution speed, which depends on in vivo dissolving of poly(DL-)lactic acid, serum concentration, and pharmacological activities.



After 5 mg of Leuprolide was mixed with a poly(DL-)lactic acid carrier by molecular dispersion, the mixture was formed into a needle-shaped compound (2 mm in diameter, 10 mm long) by fusion under pressure and heat.[14,15] This needle-shaped compound was then inserted under the skin of male rats (400 g

body weight) using double cannula needles. Pharmacological activities and the biodegradation speed of the high molecular carrier were examined by comparing the concentration of serum Leuprolide of the compound of biodegradable high molecular carrier and the ventral prostate weight (Figure 11). By the time 90 percent of the compound of the biodegradable high molecular carrier based on the poly(DL-)lactic acid with an average molecular weight 1850 (to be referred to as PLA 8 hereafter) was dissolved, most of the LH-RH agonist contained in the compound had been released. On the other hand, the other compound of biodegradable high molecular carrier based on the poly(DL-)lactic acid with an average molecular weight 2200 (to be referred to as PLA 12 hereafter) released all its LH-RH agonist in 13 weeks. When we studied the change in prostate weight as an indication of pharmacological activities, the prostate weight was reduced and suppressed for 7 weeks in the case of PLA 8 implantation. In the case of PLA 12, the prostate weight was reduced and suppressed for 11 weeks. These results indicate that the slow-releasing capability of the LH-RH agonist had been maintained over a relatively long period of about 2 months by using low-molecular weight ploy(DL-)lactic acids.

Figure 12. Variations of serum testosterone and LH values in a prostate cancer patient after a compound (PLA 8) of LH-RH agonist and biodegradable carrier was implanted.



4.2 Clinical applications -- Treatment of prostate cancers by a compound made of an LH-RH agonist and a biodegradable carrier

As was stated above, when a nonbiodegradable polymer is used as a carrier, the carrier must be removed from the body after the drug has been released because the carrier is not degraded at all in vivo. When a short-term slow release, say for one or two months, is required, it is desirable to use a carrier that

will be degraded and absorbed into the body right after the drug has been released. To treat prostate cancers with LH-RH agonists, a long-term slow release capability that maintains its release level for more than six months is required as well as a short-term release capability that maintains its level for one to two months. In order to develop a biodegradable carrier with short-term slow release capability for clinical use, a drug compound must satisfy these conditions: (1) pharmacological activities must be observable for one to two months, (2) the carrier must be completely biodegraded in three months, (3) the safety of the carrier must have been confirmed, and (4) the drug can be administered by injection. Using the poly(DL-)lactic acid as a carrier, we inserted a needle-shaped compound (PLA 8, contains 5 mg of Leuprolide) 2 mm in diameter and 10 mm long under the skin of prostate cancer patients using double cannula needles. The variations in serum testosterone and LH levels have been plotted in Figure 12. The serum LH level rose rapidly to reach a peak value in 24 hours, but it returned to the previous level after 2 weeks and then gradually fell further. The serum testosterone level peaked two days after implantation and dropped thereafter, reaching a level lower than the previous one in two weeks. In three weeks the serum testosterone level reached the range indicative of castration. These results indicate that we have succeeded in fabricating a compound of LH-RH agonists with a biodegradable carrier, which satisfy conditions (1) -- (4) stated above.

5. Closing Remarks

Our research group has been engaged in the development of slow-releasing drug carriers for several years now. In this article, we described two projects which have reached the stage of clinical applications. These projects are the development of artificial testes that release testosterone and compounds of LH-RH agonists and high molecular carriers (nonbiodegradable and biodegradable ones). In the future, our research goal is to develop slow-releasing drug carriers that have other functions in addition to slowly releasing drugs. Finally, we close this article by noting that the results presented and discussed in this article have been achieved jointly by the following members of our group:

Isao Kaetsu, Masaru Yoshida, Masaharu Asano (The Third Development Group, Takasaki Laboratory, Japan Atomic Energy Research Institute), Keiji Suzuki (Physiology Department, Medical Technology Junior College, Gumma University), Masayoshi Oya, Ryoichi Katagai (Industrial Chemistry Department, Engineering Junior College, Gumma University), Hidetoshi Yamanaka, Kyoichi Imai, Yoshiyuki Nakai, Hisako Yuasa, and Toru Mashita (Urology Department, Faculty of Medicine, Gumma University).

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CSO: 4306/1157

DEVELOPMENTS IN AGRICULTURAL BIOTECHNOLOGY DESCRIBED

Tokyo BIO INDUSTRY in Japanese Jan 86 pp 6-7

/Article by Karuyuki Kawai, Research Consultant, Japan Agriculture, Forestry, and Fisheries Technical Information Association: "Toward the Development of Biotechnology in Agriculture: An Overview"/

/Text/ For the first time in history a technology has evoked great interest and given rise to a boom that transcends national borders, all industrial fields, and extends to the civilian consumer society. I believe that this biotechnology is probably a phenomenon which will endure.

There are a variety of reasons for this phenomenon, but I think that the greatest and most basic reason beyond all others is that the very technology of biotechnology is itself extremely revolutionary. Biotechnology is revolutionary because it has its origin in the technology which reaches to the source of the biological structure of an organism. That is the rationale behind making the scholarly field of inquiry for biotechnology a broad one that crosses borders.

It is also the reason for a common field of research for medicine, physics and engineering, and agriculture. Therefore, it is comprised of fields that have a broad impact on human life and livelihood, industry, food, energy, and environmental problems. To put this another way, for business, it is the creation of new business opportunities that are broad in scope, and has resulted in the formation of a wide base for new agribusiness. I think that the greatest reason for this lies in the great expectation that biotechnology will become the typical flourishing industry of the 21st century, the post-electronics era.

A second reason for the "bio-boom" is that it is a fiercely competitive field internationally. The Office of Technology Assessment (OTA), which is an agency of the U.S. Congress, has so far twice published reports on biotechnology. The first was "Impacts of Applied Genetics," published in 1981. The second was "Commercial Biotechnology," published in 1984. In the first report of four years ago, the ability of the various countries in the world to develop biotechnology was compared. The United States took the top spot, Europe was in second place, and Japan was in third place, 5 to 6 years behind the leaders. In the second report of 2 years

ago the United States was still the leader, but there was absolutely no proof of its ability to stay in the lead in the future. Japan was in second place and was rapidly becoming a threat to the superiority of the United States. It was noted that Europe was evaluated frankly and given third place, having fallen off considerably. Indeed, this international comparison was about the commercialization of biotechnology. With regard to the progress of basic research, the United States held first place, Europe second, and Japan third, lagging considerably. Moreover, by stating that "Japan relies heavily on the United States and Great Britain in basic research," the same report clearly pointed out the tardiness of Japanese basic research.

Today it is common knowledge that the superiority of biotechnology in the future will be largely governed by the degree of depth of basic research. In the future, Japan's national research institutes and universities and the research organs of private companies must stir themselves significantly with regard to this point. In order to construct a research system that will have balance in the broad realm from basic research to applied commercial research, appropriate support measures are needed from the government in particular to help build a skilled cooperative alliance among industry, government, and academe.

The bio-boom is spreading like wildfire across all of Japan, and overall expectations of biotechnology are surging. On the other hand, research and development in biotechnology are just beginning in the agricultural field. In agriculture, many difficult problems derive from the fact that higher plants and animals are the subjects of biotechnology, and this will mean that many fields will require a sufficiently long period of gestation. However, judging from the course of the current boom, even though waiting another 10 or 20 years would be desirable, general acceptance of that would be difficult, and I think that a strategic concept has become necessary.

What is known as biotechnology is one comprehensive technological realm, and it includes many basic technological fields. If we were to categorize those fields by stages, the first stage would be the basic technology group which is already capable of commercialization. For example, this would include bioreactors and other organic cultivation, the transplant of fertile eggs of domestic animals, and the all-female technology for the sexual conversion of fish. I think that working to promote the commercialization of these first stage technologies is the most important task at hand today. Several years after this, cell fusion technology and technology to develop the use of microorganisms will be commercialized as the second stage. Another few years after that, or within a decade, it is believed that we will be greeting the commercialization of genetic recombinant technology as the third stage. This will be a consequence of the commercialization of the first stage building an enterprise base for the smooth development of the second stage, and that stage, in turn, for the third stage.

It would appear that the general public simply understands that practical results (such as superior products) are brought about directly by biotechnology. However, I think that it is significant to recognize that this is not the case insofar as genetic recombinant technology and cell fusion technology are concerned. In short, what is produced thereby is strictly a simple breeder and unless it is cross-bred to improve an already existing economic product, a useful economic product will not emerge. This is shown by the research results of the "pomato" and the tobacco tomato. This means that, in terms of modern breeding by biotechnology, cooperation between biotechnology researchers and existing breeding researchers will be extremely important at the final stage.

All parts of the country are hastening biotechnology research systems. This appears to be occurring at the expense of existing breeding research systems. It must be noted that these sorts of makeshift measures, in the end, not only hinder the health development of biotechnology, but are likely to frustrate current breeding activities.

I fully believe that for biotechnology, the revolutionary giant of a technology that has arrived at the end of the 20th century, to continue to nurture skillfully the new agribusiness, the most important thing is not to move too fast, not to lose our balance, and to create an atmosphere and conditions wherein we do not fear failure.

(The author formerly was the Director of the Agricultural Experiment Station, Ministry of Agricultural and and Forestry.)

12259/12276
CSO: 4306/1162

MANAGEMENT OF PLANT GENETICS RESOURCES FOR BIOTECHNOLOGY

Tokyo BIO INDUSTRY in Japanese Jan 86 pp 37-43

[Article by Kineo Kumagai, chief of research and development division, Agriculture, Forestry and Fishery Technology Information Association: "Gene Resources and Biotechnology"]

[Text] In biotechnology, which has developed rapidly with the support of the progress of the life science, great expectations are also being held in the field of the breeding of higher plants and from the standpoint of establishing the basic conditions, the urgency of securing gene resouces is being emphasized. Gene resources, which are the products of biological advancement and which have inscribed a history of crop improvements through DNA [deoxyribonucleic acid], will further increase their value with the progress of biotechnology and expectations are being laid on their appropriate management and effective utilization.

1. Introduction

The words, "gene resources," together with expressions like, "gene bank," have become quite familiar, in general, as they are being used daily in the mass media and, on frequent occasions, even in administrative matters to promote policies. They appear frequently in discussions on innovative advanced technologies concerning life forms, such as life sciences and biotechnologies, and therefore, it is believed that there are many persons who can analogize and understand the close relationships between gene resources and biotechnology.

The task that was given to this writer in this special article is, in the light of this background, to deepen the awareness of the true relationships between these two subjects and to provide comments which will be useful in understanding the present situation. Therefore, since biotechnology is said to be, in one respect, the technology of manipulating genes, to reveal to what extent the utilization of the resource values of the said genes is possible with the present technological level and to comment on its industrial significance and future outlook will probably meet the wishes of the editor.

However, with regard to biotechnology in the agricultural field, particularly with respect to plants, which is the focus of this article, it cannot be said

that the accumulation of technological developments concerning genes and the genetic code which controls the special characteristics of organisms is necessarily adedquate as compared with the fields of microorganism and animals. In other words, among higher plants, with regard to crops which are used as productive substances in agriculture, particularly with respect to the important characteristics of harvest yield and disease resistence in the genetic variations of breeding materials needed to improve them, it cannot be said that sufficient progress has been made in the clarification of the mechanisms of gene code manifestations and in the technological development to freely manipulate them so that they can be called gene resources.

Therefore, I would like to explain at the beginning that out of respect for the editor's wish which reflects the modern trend, the expression "gene resources" will be used, as is, in the title but in the text, the term "plant genetic resources," used in the traditional breeding field which might be called the "old biotechnology," will be used more frequently then "gene resources" of the "new technology," and that the two terms are being used with the realization that there is slight difference in the nuances of their meanings.

2. Life Science and Gene Resources

On 10 August 1984, the government announced the "Fundamental Research and Development Plan for Leading Basic Technologies in Life Science." This plan was formulated on the basis of the reply to inquiry No 10 deliberated upon by the Science and Technology Commission and was presented to the prime minister on 24 April 1984, after deliberations of over 2 years since November 1981 by the Life Science Division of the said commission.

As is known, the fundamental plan is made up of the following four chapters: (1)basic thinking; (2) expectant fields for development of "leading basic technologies"; (3) R&D areas and objectives on which emphasis should be laid at present; and (4) policies to promote accomplishment of objectives. In the supplement, as concrete examples of "R&D areas and objectives on which emphasis should be laid at present," four basic technologies are identified and the direction and methods of development are specified.

Fields in which new developments are expected through advancement of "leading basic technologies" include the following: (1) basic biology-related fields, etc.; (2) health-and medical-related fields; (3) fields related to environmental protection; (4) food-related fields; (5) resource-and energy-related fields; and (6) fields related to chemical industries. As a field in which new applications are expected, the information-related field, such as computers, is given.

Furthermore, in "policies to promote accomplishment of objectives," the following are discussed: (1) strengthening of the R&D setup; (2) training and maintenance of personnel; (3) procurement of sufficient R&D funds, etc.; (4) strengthening of R&D support setup; and (5) international exchange. In the fourth item on strengthening of support setup, the importance of securing and

supply microorganisms as gene resources and their related data is taken up at the beginning.

Although the above explanation became somewhat wordy, by guiding an overall view of the essential points in the fundamental plan of life science's R&D, one can see how important the procurement of gene resources is considered as the basic condition to promote the R&D of life science, which is said to be the basic science for biotechnology, within the nation's policies to promote science and technology. Needless to say, the gene resources identified in the fundatmental plan not only include the plant genetic resources mentioned by this writer in the earlier section but cover a much wider scope. Furthermore, as fields in which new developments are anticipated through R&D of "leading basic technologies," fields related to environmental protection and foodstuffs are given and since these are closely related to agriculture, it is correct to assume that the close relationship between biotechnology in the agricultural field and gene resources is recognized strongly in the nation's fundamental S&T policy.

3. Importance and Background of Securing Gene Resources

I believe that the NHK [Japan Broadcasting Corp] programs broadcasted in February 1982, "Age of Grain Struggle" and "A Grain of Seed Changes the World" in the series on "Conditions of Japan," had a great impact on Japan's popular opinion, which was in a very belated state as compared with that of the world's leading countries, concerning the importance of the systematic preservation of microorganisms as gene resources.

As the third in the large-scale series on "Conditions of Japan," NHK took up the food problem and in the program titled, "Food--The Earth Warns," the above mentioned two subjects were shown for which there was a particular reason, which was, "to focus attention on crop seeds which hold the key to future food problems, to portray what is happening in the world, at present, concerning seeds and to make the people seriously consider what significance that has on the Japanese and on mankind.

Surveying the background of the times which led to the concept of such a program, one finds that in January 1980, 2 years prior, the U.S. President had revealed measures to restrict grain exports to the USSR and established the diplomacy of "food as a strategic commodity," while in the U.S. industrial world, a lone venture business had entered the biotech industries dominated by pharmaceutical companies, which are huge, world-wide enterprises, and started substance production, based on microorganism and culture cells, which drew attention to its future potentials in the pharmaceutical and fementation industries. In other words, the bio-fever had begun. Also, on the occasion of the oil shocks, major international oil and grain companies began to focus on bio-industries as survival strategy with the outlook on the 21st century and the age of trials for the seed and seedling industries had arrived. Furthermore, the rapid advancement of R&D in the life science, which is the foundation of bio-industries, led to progress of molecular genetics and development of biotechnology, which had been centered hitherto on microorganisms, and as the technology of manipulating genes and artificially

controlling gene codes, they began to be applied to higher plants bringing expectations of unlimited possibilities in variety improvements of crops and big dreams to the future potentials of seed and seedling industries.

Domestically, with the establishment of the seed and seedling law, the development of new crop varieties drew the interests of enterpreneurs as investment prospects while elsewhere, the pressure of explosive population increases of developing countries, principally in Asia, aroused a sense of crisis in future food problems, and created the opportunity to attract civilian enterprises to breeding, which is the basic technology of agricultural production, and for which the government had hitherto assumed full responsibility. Moreover, the lesson that food was a strategic commodity encouraged the reappraisal of agriculture as a national security measure and the mood gradually surfaced to seriously and earnestly consider the food problem as a national task. As a result, the importance of securing seeds (gene resources, plant genetic resources, genetic code), which is the basic and most fundamental factor, was reconfirmed and the strong outcry began to the need for Japan to reflect on its lack of efforts in the past and the necessity of aggressive policies in the future.

As a noticeable action after the broadcasts, the mass media example of ASAHI SHIMBUN can be cited for carrying the special weekly installments, from July to December 1982, on "Food--What is Happening Now?" Even in the field of politics, the lifeline of which is to alert reflect trends in public opinion, the problem of seeds, which seems very conservative at a glance, began to be taken up as a political issue under the new fashion guise of "bio." The "proposal concerning procurement of biological resources to promote bioscience" by the Diet member's bioscience conference is a concrete example which was announced in December of the same year. As a concrete policy objective, the procurement of genetic resources began to be discussed in the political arena and the first step was taken toward its realization. Whatever the direct causal relations with this proposal, the director general of the Science and Technology Agency [STA] assigned in April 1983, the subject, "on procurement policy of living organisms as genetic resources," to the agency's standing Resources Investigation Committee and requested deliberations on concrete measures. To handle the official query, the Resources Investigation committee formed a "Special Committee on Genetic Resources," and began deliberations. On a lower level, subcommittees on plants, animals and microorganisms were formed and through a working group, collection, collation, etc of related materials were performed and concrete deliberations were conducted. Earnest discussions were held and in the usually short period of 1 year, the report was prepared and presented on 26 April of the following year to the STA director general.

On the other hand, because it holds the responsibility for breeding of agricultural crops, the Ministry of Agriculture, Forestry and Fishery [MAFF] had handled aggressively, from the past, the tasks of procurring genetic resources as breeding materials and their effective utilization in breeding but to respond to the rising public opinion and the supplementary resolutions adopted at the time of the establishment of the seed and seedling law, the MAFF showed a positive attitude toward the problem. That is, it reappraised

thoroughly the "project to augment the setup for preservation and introduction of seeds and seedlings" on which it had labored assiduously since FY65 and from FY83, increasing the budget three times over the preceeding year, it switched the project to "establishment of a comprehensive management and utilization system of crop gene resources and breeding information.

The MAFF's awareness of the significance of gene resources in breeding is shown in the basic breeding plan formulated in FY75 and as one of the three main supports to develop the breeding function, the MAFF established the setup to collect, introduce, evaluate and preserve seed varieties and strains as genetic resources and carried on an aggressive procurement policy.

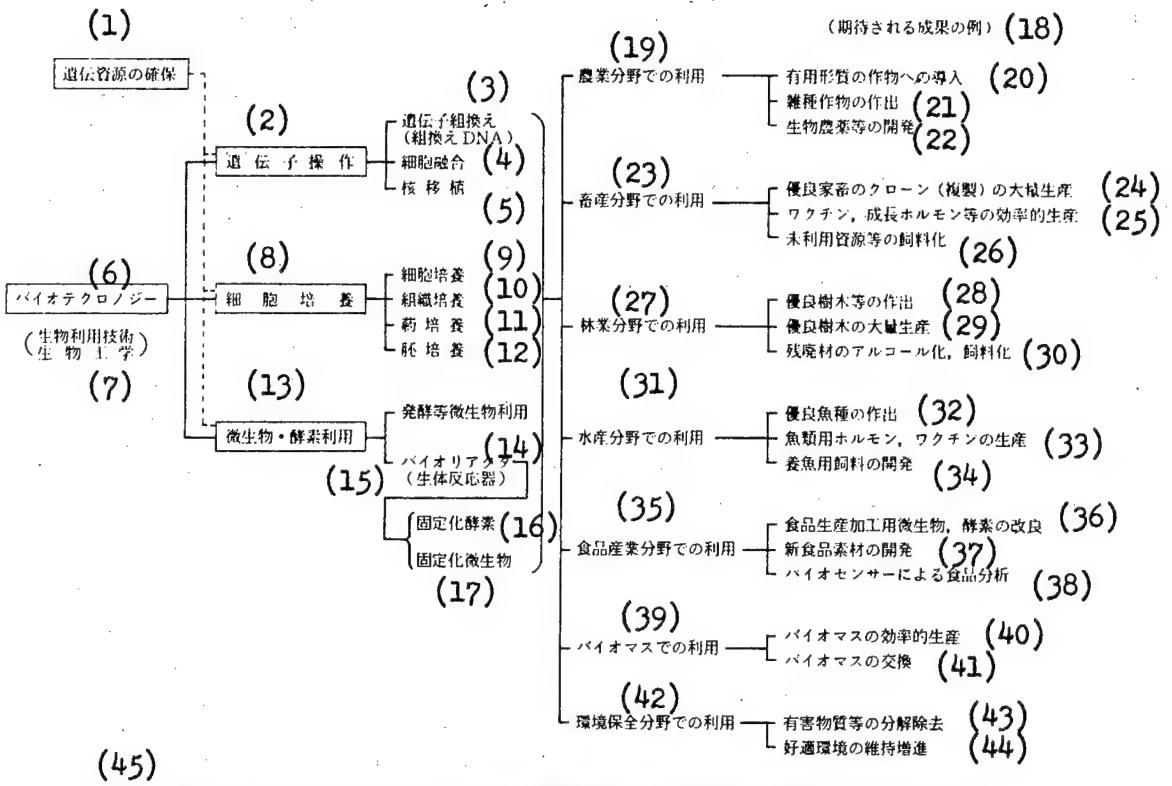
It is stated in the aformentioned report to the STA director general that the formulation of a procurement plan for genetic resources as a national policy is an urgent task and rallying around this, various ministries and agencies are planning the advancement of concrete measures in the FY85 budget in accordance with the divisional assignments of the policy. The MAFF will start the MAFF gene bank project this year and while promoting the advancement of this project, it has decided to disseminate the gene resources in its custory to users outside of the ministry and is making preparations steadily.

4. Biotechnology in Agriculture

The definition of biotechnology differs somewhat according to persons and counties but a first, it was mainly concerned with the fermentation industry or cell culture of animals and plants and substance production through micoorganisms, etc. and its application in the agricultural field was not fully realized. Naturally, since the definition of a word is prescribed by the scope and contents of its description, the meaning of biotechnology has changed with its own technological advancement and the progress of life science, its basic sciences.

The MAFF inaugurated the "Organic Resources Development and Utilization Research Committee" in FY82 and according to the report compiled after 14 months of study, it claims that it [biotechnology] is a general term for "technology to effectively utilize living organisms and the functions they possess." From the standpoint that aggressive promotion of the development and uses of organic resources through biotechnology is vital to assure a stable supply of the nation's foodstuff and effective utilization of energy resources, it was deemed necessary to hasten the augmentation of the R&D setup for innovative, advanced technologies covering the wide field of utilization of living organisms, including the fields of agriculture-forestry-fishery industries,food industries and even environmental protection. (refer to Figure 1).

Figure 1. Fields Related to Biotechnology



出所：宮元均(1982)，バイオテクノロジーによる生物資源の開発利用の推進，農林水産省広報，1982，11，p. 8－12

Key:

1. Procurement of genetic resources
2. Gene manipulation
3. Gene recombination (recombined DNA)
4. Cell fusion
5. Nuclei transplant
6. Biotechnology
7. (Technology to use living organisms
8. Cell culture
9. Cell culture
10. Tissue culture
11. Bacteria culture
12. Embryo culture
13. Utilization of microorganisms, enzymes
14. Utilization of fermented, etc. microorganisms
15. Bio-reactor
16. Immobilized enzymes
17. Immobilized microorganisms
18. Examples of expectant results
19. Use in agricultural field
20. Introduction in useful crops
21. Development of hybrid crops
22. Development of bio-agricultural chemicals
23. Use in livestock breeding

[Key continued on following page]

24. Mass production of clones of excellent livestock
25. Effective production of vaccines, growth hormones, etc.
26. Using new resources as fodder
27. Use in forestry field
28. Development of excellent trees, etc.
29. Mass production of excellent trees
30. Conversion of residue materials to alcohol, fodder
31. Use in fishery field
32. Development of excellent fish species
33. Production of hormones and vaccines for fishes
34. Development of feed for fish farming
35. Use in food industry field
36. Improvements of microorganisms and enzymes for food production
37. Development of new food materials
38. Food analysis with bio-sensors
39. Use in biomass
40. Effective production of biomass
41. Conversion of biomass
42. Use in environmental protection field
43. Disposal of harmful materials, etc.
44. Promotion and maintenance of healthy environment
45. Source: Hitoshi Miyamoto (1982), "Advancement of Development and Uses of Biological Resources through Biotechnology," MAFF BULLETIN, November 1982, pp 8-12

Furthermore, as promotional measures for development and utilization of biological resources through biotechnolgy, the following are included: (1) establishment of a comprehensive experimental and research setup covering governmental, industrial and academic circles; (2) expansion and strengthening of the promotional setup; and (3) adequate collection and management of genetic resources. Also, as items to be handled immediately and expeditiuosly with FY83 as the target date, the following concrete measures were recommended: (1) continued advancement of R&D of "development of organic resources through cell fusion and nuclei transplants." etc. which are already being conducted; (2) aid to R&D by civilian sector breeding groups; (3) establishment of a comprehensive management and utilization system of plant genetic resources and breeding information; and (4) aggressive uses and their improvements of mobile research personnel system, commisisoned research personnel system, solicited research personnel system, etc.

From the above developments, it can be seen that in biotechnolgy in the agricultural field, improvements of living organisms, i.e., breeding is the focal point, and to accompolish that, procurement of genetic resources and their effective utilization are important and to further increase their efficiacy, accumulation of the genetic code and the establishment of setup to utilize that is indispensable.

5. Breeding and Genetic Resources

Breeding is the creation of varieties and strians with new characteristics by recombining the gene structure possessed by crop varieties and strains. In general, it is also called breed improvement but it is not only improvement on the variety level but includes the artificial creation of new species and genera of crops. Importation of new crops from foreign countries or areas

with differing climate conditions and cultivating them in a new environment is breeding and the culture of wild species or closely related species is also a function of the breeding field.

Genetics is the foundation of breeding which follows the principle that characteristics are transmitted from parents to their descendents in accordance with Mendel's laws and the advancement of breeding is largely dependent on the progress of genetics. Furthermore, to increase breeding efficiency and to attain sophisticated breeding objectives in a short period, the development of technolgy needed to improve methodology is important and both basic and applied researches are indispensable in the breeding technology.

However, the potentiality of breeding rests on whether the mating bodies to be used as breeding materials possess the characteristics desired as breeding objectives. In order to do that, it is necessary from day to day to collect, evaluate, organize and preserve genetic resources and to utilize them effectively and with advanced-breeding crops, such as rice, wheat, corn, etc., for which breeding objectives are being diversified and sophisticated, it would not be an exaggeration to say that the success or failure of breeding would be decisively swayed by whether or not an adequate supply of genetic resources has been prepared. Also, to effectively use plentiful genetic resources, it is necessary to know the history of the different varieties and strains and their special characteristics, and moreover, in order to incorporate the desired objective in the new variety, the genes and gene structures which control the characteristics must be known.

In this way, technological development in breeding and procurement of genetic resources are like the two wheels of a car and new biotechnology and genetic resources are the fundamental conditions for biological improvements in today's age of innovative, advanced technologies, but here, I shall look over the past and present a number of examples of the roles genetic resources played in the traditional breeding.

An outstanding example where a native species was beneficial in breeding was the use of the Taiwan native species, "di-jiao-wu-jian" as the parent of the IR-8 developed in the International Rice Research Institute in Manila, Philippines, and the result propelled a green revolution in Southeast Asia. In cultured varieties, Japan's wheat "Norin No 10" was taken to the United States after WWII and used as the breeding parent of a low, short-stalk variety and its descendants created a series of Mexican Wheat, which rescued India and Iran from famine as well as contributed greatly to raising wheat production in the world. Now, it is known that the genes which determined the stalk height were contained in the variety called "Daruma," which is the parent of "Norin No 10," and the transmissin method has been analyzed but wheat growers throughout the world know that the process to put the genes in the new variety required a great deal of effort. The American professor Borlaug [Norman E.], who had worked principally on the breeding, won the Nobel Peace Prize for his achievements while the wheat, Norin No 10," which was not too highly evaluated in Japan, became famous overnight throughout the world.

Through local strains cultivated principally in the Kanto region, the rice variety called, "li-chih-chiang," introduced form China was used for secondary breeding of a cold-resistant variety for the Tohoku and Hokaido districts and the rice strains which originated in a tropical region contributed to pushing the northern limits for cultivation. Also, the Indian varieties introduced from Southeast Asia and Indonesia have contributed immensely to increasing the disease and insect resistance of rice and in breeding, the importance of imported genetic resources is equal to that of native and cultivated species.

If one recalls the successful accounts of intercontinental transmittal of crops, such as rubber, cocoa, coffee, etc., which greatly changed the face of the world's industrial map, the stories of arrival to Japan in ancient times of sweet and Irish potatoes and the recent popularity in the market of Kiwi fruits and Chinese vegetables, one can readily understand the great influence in our lives of the direct uses of imported farm products.

6. Management of Genetic Resources

The objective of genetic resource management is the maintenance and preservation of useful gene variations of living organisms so that they can be used effectively in breeding but depend on the varieties categorized by the genes they possess or the seeds and nutrients of the strains, there are stages where the "substances" themselves are handled and where the "code" which symbolizes them are handled.

Recently, the importance of securing genetic resources has begun to be emphasized and the urgency of preserving and maintaining them is being talked about so I would like to touch briefly on their background factors.

Just as the regions in which agriculture began were limited on earth, so are there cradles of origin for the various crops and since many gene variations can be ascertained in those regions, they are called the gene centers. According to the Soviet botanist Vavilov [Nikokai Ivanovich], there are eight big centers in the world and the types of crops which originated there are known. Heretofore, through plant searches and collections in those gene centers, new genes needed for breeding were readily obtainable but recently, the decrease and dry up of variations in those centers have become noticeable and the loss of valuable genetic resources has become of concern. Also, in primitive forests of tropical regions, many plants thrive and are seen as treasures of plant resources but because of disorderly and unplanned lumbering, not only rare plant species but many animals and microorganisms living there ar being exterminated at the same time and with the destruction of ecological balance and the vegetation changes, there is danger that, in extreme cases, they might become deserts.

The IBPGR (International Board for Plant Genetic Resources) believes that this world situation will beckon raid losses of gene resources which are the common earth resources of mankind and cast as dark, grave and irreversible shadow on the future food problem and is advocating the expeditious collection and maintenance/preservation of available gene variations. As concrete actions, it is recommending that the world be divided into a number of regions, that

selections be made of areas which should be searched immediately and that priorities be placed on crops in the respective regions, and though technological and financial assistance with the close cooperation of the concerned countries, conduct search and collection activities aggressively.

The dissemination over a wide area of cultured varieties with excellent characteristics contributes to the improvement of agricultural production, itself, and serves the welfare of mankind but on the other hand, it leads to unification of species and results in the loss of genetic diversification. In other worlds, it injects the problem of the genetic weakness of crop species and leads to the deterioration of the crop's compensatory power against disasters and weakening of resistance against new bacterial strains of diseases. The terrible experiences of the problems created by the considerable damages suffered by the U.S. corn using the F_1 hybrid and the species resistant to the rice blight among the Japanese rice are still fresh in the memories of those who were concerned.

In order to perform appropriate management of genetic resources, it is necessary to consider the relationships between mankind and plants from the historical beginnings. That is the problem of the origin of agriculture and the problem of the history of plant culture. That involves the problem of how our ancestors labored to identify edible plants, how they switched from a life of hunting, gathering and nomadism to a settled life of farming in one area by succeeding in the cultivation of wild plants, how much they labored on improvements to increase the productivity of the crops and as a result, how they succeeded in building up the culture which only mankind possesses.

Resting on the history of coexistence between mankind and plants, the preservation and management of genetic resources must maintain the genetic variations of living plants in the most usable form and supply expeditiously the genes needed to meet the objectives of breeding and it can be said that the means to provide the "hardware" and "software" to realize this is the "gene bank." Therefore, among the functions of the gene bank are the strategic thinking to preserve natural surroundings abundant in gene variations, such as gene centers, and to protect the genes under natural conditions, the preservation and maintenance of genetic resources transferred to artificially controlled environment (under cultivation in gardens or under culture in protective facilities such as greenhouses, netted houses, laboratories, etc., artificially controlled environment such as fixed-temperature containers, freezers, etc. and in test tubes, flasks, etc.) in a form that can be utilized readily in breeding and to maintain a setup which can provide them on a timely and unerring basis together with the necessary data. To attain this aim, a "genetic resources center" should be established to systematize the management system for substances and codes and promote the R&D aspects so that the genes can contribute even more to breeding and that both functions be exercised with proper coordination. Such a move is desirable and its development is anticipated.

7. Conclusion

Through the advancement of biotechnology, the exchange of genetic codes of living organisms has exceeded the bounds of reproduction within species and not only made possible methods for interspecific and intergeneric reproductions, but with the use of animal and plant genes as microorganisms and the fusion of plant and animal cells, it is about to break the barriers separating the kingdoms of living forms (animals, plants and microorganisms). As a result, the appearance of new organic substances which did not exist heretofore in not a dream and in reality, beginning with the "pomato" which is a hybrid of tomato and potato, new intergeneric plants, such as carrots and parsley, Whitlow grass and rape, etc., and hybrids between wild and cultured species, the cross-breeding of which had been considered impossible, are being grown abundantly.

This biotechnological advancement is being sustained by the rapid progress and development of the so-called life sciences, such as molecular biology and molecular genetics, and the life phenomenon and genetic principles of living organisms have come to be understood coherently form microorganisms to human beings as material objects of physical and chemical mechanisms.

Consequently, the possibility of using gene recogination and cell fusion as means to breed higher plants has become promising and the age when stored genes (DNA particles) can be used directly in the improvement of living forms is probably not too far off. That is, when it becomes possible to know about the genes which control specific characteristics from the standpoint of the genetic code as expressed by three combinations of four different bases of DNA (deoxyribonucleic acid) and to manipulate precisely their effects on character manifestations by controlling their structures and control mechanisms, then, the existence of a gene library for higher plants becomes a reality and the gene bank can display its functions literally. Until then, it is perhaps wiser to call the materials for gene variations in plant breeding a plant genetic resources rather than gene resources.

9134/13068
CSO: 4306/1164

COMPUTER CONTROL OF FERMENTATION PROCESS OF SAKE

Tokyo BIO INDUSTRY in Japanese Feb 86 pp 5-12

[Article: "Computer Control of Sake-Moromi Fermentation"]

[Text] Sake-moromi is a complex system of simultaneous multiple fermentation processes in which enzymatic dissolution of cooked rice and fermentation of alcohol by yeast and enzyme proceed simultaneously. Traditionally, this kind of fermentation process has been controlled through experience and feeling. In order to modernize the sake-moromi fermentation process, this multiple fermentation process was analyzed from the standpoint of reaction kinetics. Using a simplified rate equation, a computer program was developed for automatic control.

1. Introduction

Brewing, including sake, is really the root of biotechnology. From the early days of history, the brewing technology has been a traditional industry handed down primarily as empirical know-how. Manufacturing of sake has been handled by a special group of technicians called Toji (sake-brewers). This group focused on refining the technology for improving the quality rather than on productivity.

Under the "age of enlightenment" brought on by the Meiji restoration, many researchers and technologists turned then scientific attention to the traditional technologies. Based on microbiology, analytical chemistry on the fermentation science approach, they exhaustively strove for a scientific understanding of method and for quality improvement. However, brewing involves complex and intricate factors, and as a result, researchers have been bogged down with difficulties in understanding the fermentation mechanism and the formation of aromatic components. Thus, the fermentation technology has inevitably remained a mystic art.

For brewing sake, which is primarily dictated by microbiological action, the merit of the handmade process is not really a viable concept to be considered seriously. However, the conceptual image of the old inefficient brewing method has been called handmade process and respected as such. This kind of understanding of the brewing as an artistic and handmade industry is responsible for the delay of modernization of the sake brewing industry.

Like other food processing industries, the sake brewing industry has also been swept by the modernization wave. Over the last decade or so, production rationalization (optimization) and automation have been gradually achieved in the brewing industry.

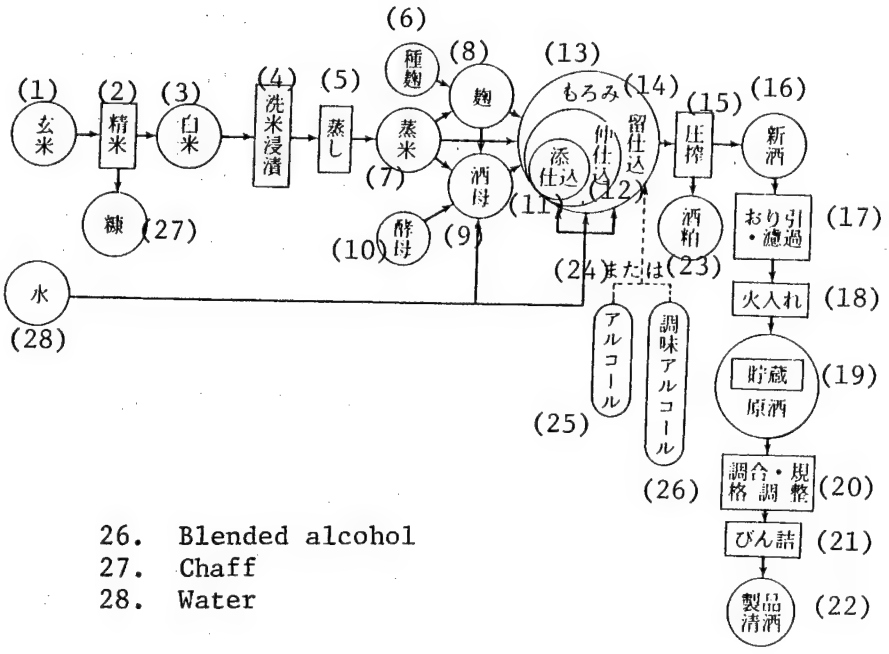
Figure 1 shows a flow diagram of the sake brewing processes. Some of the important processes have already been automated; polishing rice, steam cooking rice, and press molding the malt. The technology to produce rice malt by machine is rather advanced. Yeast is the starter for moromi fermentation. But nowadays yeast is also being prepared by the pure yeast fermentation method. In this manner the modernization of the brewing industry has advanced to some extent. This does not mean that the modernization of the brewing processes is linked to deterioration in quality; on the contrary, it is linked to improvement of the quality of the product.

This paper presents a discussion of sake-moromi fermentation control (automatic fermentation control process) research about which has not advanced a great deal.

Figure 1. Sake manufacturing processes

Key:

1. Unpolished rice (brown rice)
2. Polished rice
3. White rice
4. Rice cleaning
5. Steam cooking
6. Seed malt
7. Steamed rice
8. Malt
9. Yeast
10. Yeast
11. Loading
12. Interim loading
13. Moromi unloading
14. Moromi unloading
15. Press molding
16. Fresh sake
17. Filtering
18. Firing
19. Storage of pure sake
20. Blending and adjusting to specifications
21. Bottling
22. Final product
23. Dregs
24. Alcohol
26. Blended alcohol
27. Chaff
28. Water



2. Simultaneous Compound Fermentation

Sake-moromi fermentation is unique in that two major processes proceed simultaneously; dissolution of steamed rice by enzyme, and alcohol synthesis by saccharination and yeast. This is called simultaneous compound fermentation. Contrasted to this kind of process, beer brewing proceeds by stages in which the saccharination and fermentation of the barley liquor take place as separate processes. This is called single compound fermentation. Simultaneous compound fermentation of sake-moromi is a form of continuous fermentation process although feed stock supply and the product handling processes are not continuous. That is to say, glucose, the basic material for alcohol fermentation, is continually generated from the steamed rice by the action of oxygen, and the glucose thus generated is immediately and continuously converted into alcohol by yeast. Except at the beginning of the reaction, the yeast concentration remains almost constant throughout the reaction. (2 to 3×10^8/ml).

The concept of simultaneous compound fermentation has existed since the old days, but quantitative and analytical understanding of the kinetics and reaction mechanism have not been available until recently. Sake-moromi is not a homogeneous mixture of steamed rice, malt and water, and this makes analysis difficult.

Mikichi et al.[1,3] and Nagatani et al.[4,5] obtained some valuable background data. This author, with others, has made a comprehensive analysis of this simultaneous compound fermentation process by analyzing the function of each enzyme and its interaction with other enzymes in the system and we were able to present the reaction mechanism in a simplified form. The simultaneous compound fermentation process was categorized into three major reaction steps for performing kinetic analysis; 1) dissolution of steamed rice involving alpha-amylase, 2) formation of glucose involving glucoamylase, and 3) formation of alcohol involving yeast.[6]

2.1 Dissolution of Steamed Rice

The dissolving of steamed rice was found to follow approximately the rate equation shown by formula (1).

$$-ds/dt = k \cdot \Sigma_a^{\alpha} \cdot S \qquad (1)$$

Where, S : steamed rice (g)

t : Time (days)

Ea: Activation energy of α -amylase (U/g white rice)

k : Rate constant

α : approximately 0.2

The above formula is obviously a simplified form. The fermentation activation (Ea) energy is reduced or even inactivated, as the moromi fermentation proceeds.

The rate constant $k(1/U^{0.2}/day)$ is determined through experimental data, and the values are tabulated in Table 1. The data shows that the reaction follows the Arrhenius' equation very well, and the rate equation can be expressed by formula (2). Determining a non-homogeneous reaction may lack rigor, but, for the present - Formula (2)

$$k = a \cdot \exp(-E/RT) \qquad (2)$$

where, a : rate constant (3.38×10^{12})

E : Activation energy (18,000 cal/mol)

R : Gas constant (1.987 cal/mol/°K)

T : Temperature (°K)

It should be pointed out that Formula (2) is an approximation because the reaction system we are dealing with is an non-homogeneous system whereas the Arrhenius' equation was derived for a homogeneous system. From Formula (2), the activation energy, E, was obtained to be about 18 kcal/mol. Table 1 shows steamed rice dissolving rate (g/g of white rice/day) obtained from Formula (1) with respect to each alpha-amylase level based on the k values obtained from Formula (1).

The value of alpha can be determined from the experimental data but varies depending on the nature of the moromi. In this example, alpha was given a value of 0.2, but in some other cases a value of 0.25 may very well fit the condition. At any rate, it is important to note that the value of alpha is much smaller than one. As a result, some variation of the α -amylase content does not affect the rate of dissolution of the steamed rice. This further suggests that melt alpha-amylase adheres very well on the surface of steamed rice. This subject matter is currently under active investigation[7] but is not directly connected to the main thesis in this paper and will not be discussed here.

2.2 Formation of Glucose

Glucose formation is believed to be proportional to the amount of glucoamylase according to Formula (3)

$$dG/dt = k, \ ^{\circ}Eg \cdot \exp(-k_2 t) \qquad (3)$$

Where, G : Amount of glucose (mg)

k_1, k_2 : constants

Eg : Initial glucoamylase strength (U/g white rice)

t : time (days)

Glucose formation up to the half-life of the moromi follows roughly a linear relationship, and the exponential term (correction term) can be neglected. Thus, glucose formation really follows a 0th order reaction kinetics. As shown in Table 2, the rate of glucose formation is approximately an order of magnitude lower than that of dissolution of steamed rice. This is probably because the feedstock supply for glucose amylase is present in excess.

This value of k_1(mg/U/day) is obtained from experimental data. Table 2 shows the rate of each glucose amylase formation obtained from Formula (3) based on the experimental values of k. The rate constant was found to follow the Arrhenius' equation. Based on these inputs apparent activation energy was found to be about 18 kcal/mol which is equivalent to that for the dissolution of the steamed rice.

2.3 Formation of Alcohol

Of course, alcohol formation takes place by yeast. The formation of alcohol follows a roughly straight line relationship up to the half-life of moromi. The rate of formation is given by Formula (4).

$$dA/dt = k_a \cdot N \tag{4}$$

Where, a : Alcohol volume (mg glucose)

k_a : rate constant

t : Time (day)

N : yeast number

In the case of sake-moromi, the yeast number reaches a constant level within 2 to 3 days, and the alcohol formation from that point becomes linear.

Table 3 shows experimental data of ka·N at various temperatures and glucoamylase levels. The data indicates that the alcohol fermentation rate is determined by the glucoamylase levels. However, at levels higher than 55 Units/g white rice, the effect of the glucoamylase level on the alcohol fermentation disappears. As a result, the alcohol fermentation rate becomes constant without being affected by the glucoamylase level. This is because there is a rate determining step dictated by the glucose supply. When the glucoamylase level is low and the glucose supply is insufficient, the alcohol fermentation process is controlled by the rate determining step, and as a result, the alcohol fermentation rate is apparently governed by the glucoamylase level.

Customarily, as long as ka·N value is constant at a constant temperature condition, the k_a·N value varies according to the glucose amylase level because of the rate determining step dictated by the glucose concentration for the fermentation process. The rate dependence of the fermentation process on the glucoamylase ceases to dictate the rate at the glucoamylase levels beyond 55 Units/g-white rice. As a result, the k_a·N value is not affected by further increase in the glucoamylase level. The true value of k_a·N can be obtained in this range. Under this condition, k_a follows the Arrhenius' equation. The apparent activation energy calculated from the Arrhenius' equation was about 15k cal/mol.

2.4 Reaction Process Modeling of Simultaneous Compound Fermentation

So far, we have discussed the sake-moromi fermentation process from the standpoint of three major process steps; 1) dissolution of the steamed rice, 2)

Table 1. Initial rate of dissolving of steamed rice

Temperature	k	Alpha-Amylase (U/g-white rice)			
(°C)	($1/U^{1/5}$/day)	100	200	300	400
12	0.053	0.133	0.153	0.166	0.176
15	0.075	0.187	0.216	0.235	0.248
18	0.101	0.255	0.291	0.316	0.355

Table 2. Initial reaction rate of glucose formation

Temperature	k_1	Glucoseamylase (U/g-white rice)		
(°C)	(mg/U/day)	40	50	60
10	0.56	0.022	0.028	0.037
15	0.90	0.036	0.048	0.054
20	1.56	0.062	0.078	0.094

Table 3. Alcohol formation rate

Glucoamylase	Temperature		
(U/g-white rice)	10 C	15 C	20 C
25	0.020	0.036	0.054
40	0.026	0.045	0.064
55	0.035	0.057	0.085
70	0.035	0.058	0.080

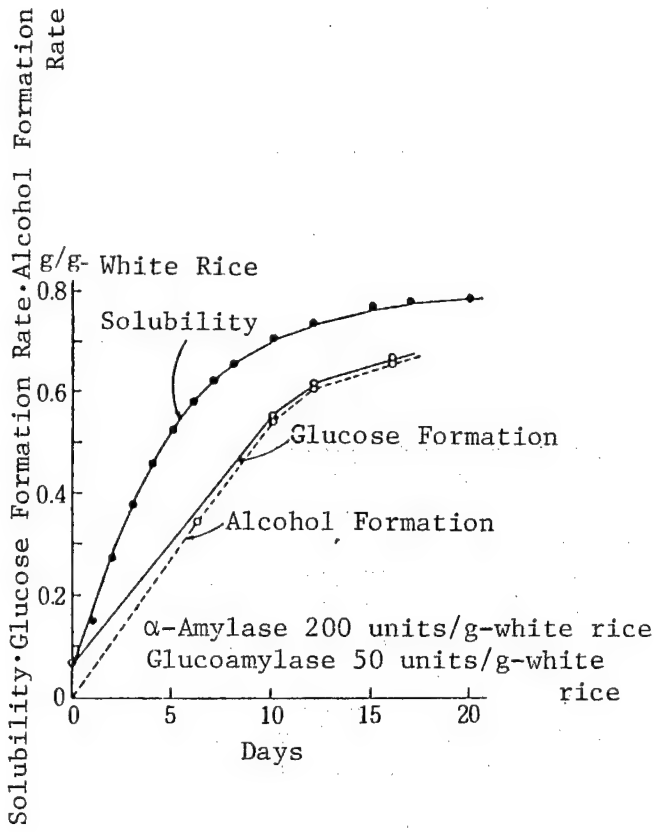
formation of glucose, and 3) alcohol formation. The results are summarized in Figure 2. For sake-moromi fermentation, first the dissolution of the steamed rice takes place, and the glucose and alcohol formation steps take place in sequence under the presence of a sufficient amount of base material. Since the alcohol fermentation rate is greater than the glucose formation rate, both of these processes usually proceed simultaneously. The interrelationship among these three major steps is greatly influenced by the enzyme balance, and therefore, enzyme strength value check becomes an important factor for the moromi fermentation control. The three major steps, dissolution of the steamed rice, glucose formation, and alcohol formation are greatly affected by temperature, but their relative formation rates remain about the same because the apparent activation energies for these three reaction steps are about the same. The temeprature simply affects the steepness of the rate versus time

curves, making the curves sharper or flatter, without disrupting the relative reaction rates at a given temperature. The temperature effect during the first two to three days needs further consideration, however, because this is the yeast breeding period. If the temperature is low, the yeast breeding slows down, and as a result, the fermentation rate becomes lower than the glucose formation rate.

But in practice, the initial temperature is low (about 10°C), and as the fermentation proceeds, the temperature is raised (15 to 18°C). Thus, real fermentation patterns are different from those shown in Figure 2 in which the fermentation curve was obtained at a constant temperature. Temperature correction can be readily obtained by Formula (2), and it is relatively easy to obtain the fermentation pattern for a real situation according to the real temperature path.

Enzyme strength value and temperature are the two major factors affecting the moromi fermentation rate. But once the feedstock is placed in a reactor tank, each enzyme strength value is fixed, and as a result, temperature becomes the only means freely to control the fermentation process. It is, however, possible to supplement the enzyme in the middle of the fermentation process.

Figure 2. Simultaneous compond fermentation model for sake-moromi. Alcohol formation rate is expressed as the glucose content corresponding to alcohol formed



3. Sake-moromi Fermentation Control

Customarily, sake-moromi fermentation control was carried out through temperature control based on the analysis of the chemical constituents (alcohol, Baume). The moromi temperature was usually controlled at the low temperature range, but once the temperature rises, the temperature was left alone. As a result, the time required for obtaining the desired chemical constituent values was delayed, and the solubility of the steamed rice was determined only after a sample was taken from the reactor and analyzed.

For designing automatic control of the moromi fermentation process, computers and sensors must be used freely. The reaction rate (transformation of the feedstock into the product) of the sake-moromi fermentation is very slow compared to other chemical reactions, and therefore, analysis of the chemical components once a day is sufficient to provide the inputs for automatic control. Therefore, it is likely that installation of sensors for a minute-by-minute monitoring of the reaction variables is not called for. However, it will be necessary to install automatic samplers and automatic analytical systems to provide inputs to the computer. The analytical data thus obtained can be fed into the computer manually.

3.1 Simulation of Dissolving of Sake-moromi

Iwano[8] developed a computer program for obtaining the rate of dissolving of sake-moromi from the relationship between the temperature and the initial alpha-amylase concentration using the rate equation for the dissolving of the steamed rice, Formula (1). When using Formula (1), the enzyme strength value, Ea, decreases as the moromi reaction proceeds, and the constant value of alpha is expected to vary. This variation needs to be corrected.

Fujita et al.[9] derived interference coefficients for the dissolving process due to glucose (C_{ig}) and due to alcohol (C_{ic}) as shown by Formula (5) and (6).

$$C_{ig} = 1 - 0.030\ G \tag{5}$$

$$C_{ie} = 1 - 0.016\ Et \tag{6}$$

Where, G : glucose concentration (%)

E_t : alcohol concentration (weight by %)

In order to derive Formulas (5) and (6), glucose and alcohol contents have to be analyzed.

In contrast to this approach, Iwano added correction terms to Formula (1) to correct the deviation of the real system from Formula (1) arising from interference to the reaction or from deactivation of the enzyme.

$$-ds/dt = k \cdot E_0^{\alpha} \exp(-k_i t) \cdot S \tag{7}$$

Where, E_o : Initial alpha-amylase activation (U/g - white rice)

k_i : Deactivation constant

k : Rate constant

d : 0,22

Iwano wrote a computer program using Formula (7), and performed simulation by suitably adjusting the k_i value. At 15°C, k_i value of 0.10 (α=0.25), and the calculated value of the degree of dissolving agreed well with the observed value.

For calculating the solubility, Formulas (8) and (9), derived by Nagatani et al.[4] were used.

$$m = v \cdot E_x \tag{8}$$

$$v = v_0 \{ 1/(1 - 0.612 E_x) \} \tag{9}$$

Where, ν : amount of dissolved moromi at a given time

ν_o : amount of dissolved moromi at start (absorbed water plus the water content in the steamed rice)

m : Amount of steamed rice dissolved (g)

Ex : Original extract (%)

Here, Ex is called the original extract and represents the total extract of the dissolved rice (alcohol is added after converting to the original glucose content). This original extract is calculated according to Formula (10) based on the alcohol content and the Japan Liquor Index (specific gravity unit for liquor.)[10]

$$E_x = E_x^0 + 1.5894 \times E_t' \tag{10}$$

$$E_x^0 = \left[\{ 1443/(1443 + M) \} - E_t'' \right] \times 260 + 0.21 \tag{11}$$

Where Ex° : Extract fraction (%)

E_t^1 : alcohol fraction (% vol)

M : Japan liquor index

E_t'' : alcohol fraction (specific gravity):15°/15°.

The amount dissolved is obtained by multiplying the original extract by the total moromi liquid. The total liquid volume (ν) is obtained by Formula (9).

Iwano prepared a computer program for determining the degree of dissolving of the steamed rice from the alcohol fraction and the Japan Liquor Index using Formulas (8)-(11). The program was adopted to a pocket computer for moromi fermentation control.

The correction term is Formula (7) corresponds to the residual activation rate (U/U°) when the variation of the activation (U) can be expressed by Formula (12).

$$-dU/dt = k_i \cdot U \tag{12}$$

treating the deactivation of the alpha-amylase as the first order reaction. Integrating Formula (12) and taking the logarithm of the integral, Formula (13) is obtained.

$$U/U^\circ = \exp(-k_i \cdot t) \tag{13}$$

In practice, alpha-amylase strength was measured daily and the k_i value was calculated. At a fermentation temperature of 16.5°C, k_i = 0.12 (U/g-white rice/day) was obtained. This k_i can be expressed according to the Arrhenius' equation as in Formula (14).

$$k_i = a' \cdot \exp(-E'/RT) \tag{14}$$

Calculated values of α' and E' were: $\alpha'=8.59\times10^{14}$ and E'=21,000 (cal/mol).

A computer program was prepared for sake-moromi fermentation process control (control of dissolution of the steamed rice) using Formulas (2),(7)-(11). The flow diagram of the program executed is shown in Figure 3. When there is a disagreement between the degree of dissolving obtained by chemical constituent values (alcohol content and Japan Liquor Index) using Formula (8)-(11) and the calculation of dissolution rate and temperature (Formulas 2,7), the value obtained by numerical analysis according to the Lunge-Gutta method (assuming alpha-amylase activation energy of 200 units), alpha-amylase activation energy is estimated by performing correction calculations for alpha-amylase.

The solubility is finally obtained as an output based on the recalculation using the corrected alpha-amylase activation energy value. Then, the expected temperature path is supplied as an input to obtain the expected solubility. If this output does not agree with the expected value, the calculation is repeated to determine the required temperature path of moromi. But in some cases it is not desirable to raise the temperature during the latter part of the moromi fermentation to maintain the sake's quality. If that is the case, a simulation calculation is performed using the enzyme strength as a variable to correct the enzyme strength value.

This program was applied in the actual hewing by a manufacturer A, and the results are shown in Table 4. The solubility obtained from the simulation agrees almost completely with that obtained from the chemical constitutent analysis values. Dreg percentage is obtained[4] by "sliding" the solubility, and the dreg percentage shows only 1 percent deviation from the experimental values.

Figure 3. Flow diagram

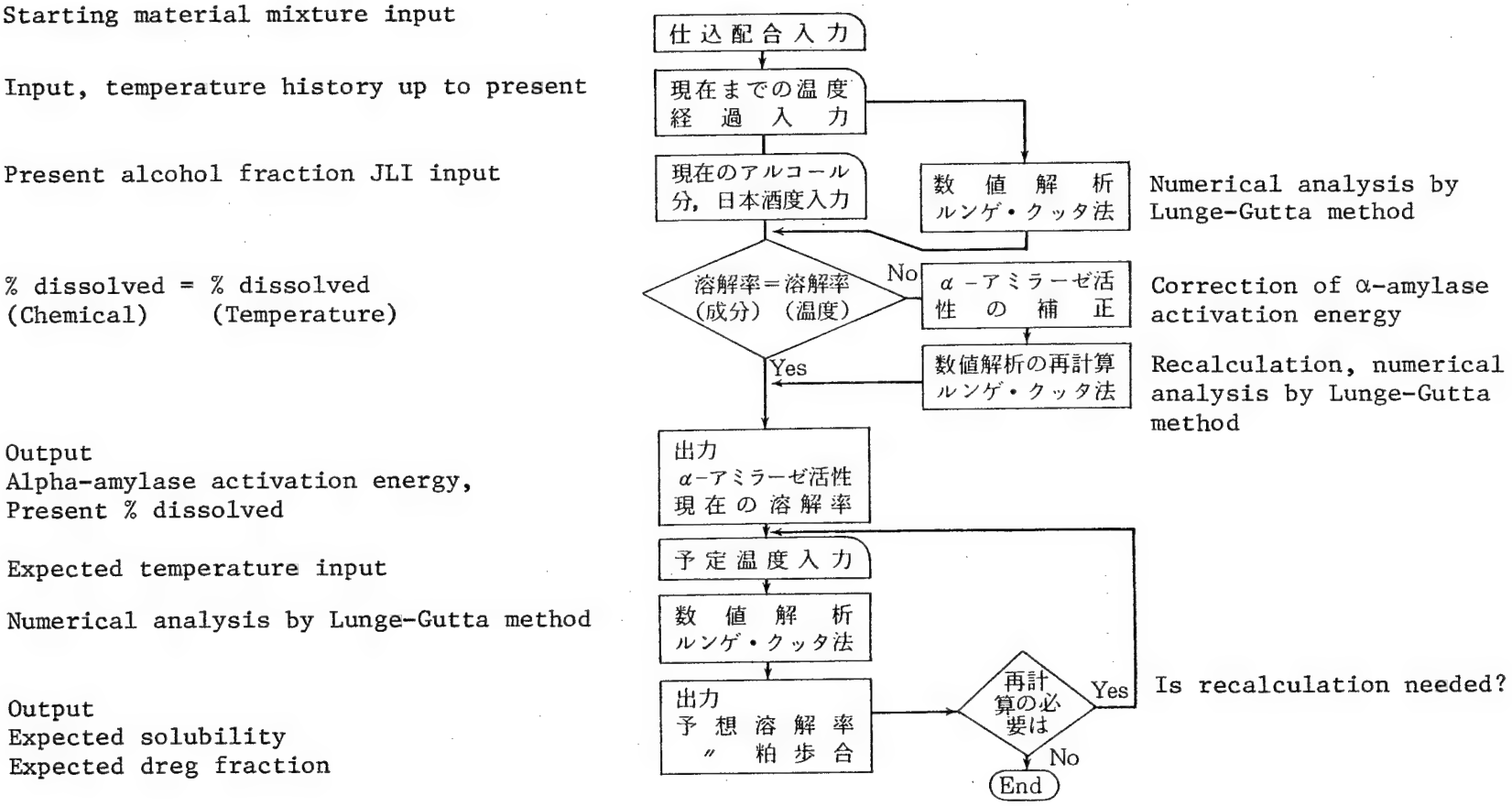


Table 4. Example (A Brewery 53BY)

Days	Product Temperature (°C)	Alcohol Content (%)	Baume (JLI)	Amount Dissolved (By Chem Analysis)	Estimated: Amount dissolved	Estimated: Dreg Percentage
醪日数	品温 (℃)	アルコール分 (%)	ボーメ (日本酒度)	溶解率 (成分)	推定値 溶解率	推定値 粕歩合
1	8.0					
2	9.0		(ボーメ)			
3	10.0		6.8			
4	11.5					
5	13.0		6.2			
6	14.0					
7	14.5		5.4			
8	15.0					
9	15.0	11.7	4.7	65.6		
10	15.0				68.2	46.7
11	15.0	14.0	3.3	69.9	70.4	41.4
12	15.0		(日本酒度)		72.1	37.0
13	15.0	16.0	−16.0	71.3	73.5	33.5
14	15.0				74.7	30.6
15	14.3	17.8	− 8.0	76.3	75.6	28.3
16	14.0				76.4	26.4
17	13.5	18.4	− 4.5	77.6	77.0	24.9
18	13.0				77.5	23.7
19	12.5	18.7	− 2.0	77.9	77.9	22.6
20	12.0	18.8	− 2.0		78.2	21.8

(Note)

Alpha-amylase activation energy was estimated from the 9th day temperature history, 9th day alcohol content, and Japan Liquor Index. Estimated value is 302 U/g-Rice (Real value, 296U/g-Rice). Using the activation energy value thus obtained, the degree of dissolving was estimated from the product temperature history. Real values were: pure alcohol yield, 356 ℓ/t, dreg percentage, 22.8 percent.

3.2 Simulation of Alcohol Concentration

Tanaka et al.[11] performed investigation using yeast which is free of No 6 bubbles (according to the Japan Fermentation Association) in order to formulate a rate equation which can predict the alcohol formation rate of sake-moromi at any given time. As a result, breeding rate equation (specific breeding state μ) and fermentation rate equation (specific alcohol formation rate ν) were obtained for a homogeneous liquid phase system: which considered the concentration of glucose, the concentration of alcohol, and the influence of temperature: Formulas (15) and (16)

$$\mu = A \cdot G/(G + K_s + G^2/K_{si}) \exp \{ K_1 E t^2 \cdot \exp(K_2 G) + K_3/T \} \quad (15)$$

$$\nu = a \cdot G/(G + k_s + G^2/k_{si}) \exp \{ k_1 E t^2 \cdot \exp(k_2 G) + k_3/T \} \quad (16)$$

Where, the units are μ (1/h) and ν (g-alcohol/g-cell/h) and,

G	:	glucose concentration (g/dl),
Et	:	alcohol concentration (g/dl),
A	:	constant (1/h),
Ks	:	saturated breeding content (g/dl),
Ksi	:	feedstock interference coefficient relative to breeding (g/dl),
K1,K2	:	alcohol interference coefficient relative to breeding (g/dl,dl/g)
K3	:	constant (°K)
α	:	constant (1/h)
k_s	:	alcohol formation saturation constant (g/dl)
k_{si}	:	feedstock interference coefficient relative to alcohol formation (g/dl)
k_1,k_2	:	alcohol interference coefficient relative to alcohol formation (dl^2/g^2,dl/g).

Specific breeding rate (μs) and specific fermentation rate (ν_s) of sake-moromi were obtained, taking into consideration of the effect of yeast bacteria concentration on the yeast breeding speed and specific fermentation rate during the breeding period.

$$\mu_s = \mu(1 - X/X_m) \quad (17)$$

$$\nu_s = \nu + a \cdot \mu_s \quad (18)$$

Where,

X : Cell concentration (10^8 cells/ml)

Xm : Maximum cell concentration (10^8 cells/ml)

α : Constant (g-alcohol/g-cell)

Using Formulas (15-(18), laboratory scale simulation was completed with good results for estimating variations of the moromi-yeast and the alcohol concentration at any given time. It is, however, necessary to measure glucose content, alcohol content, and the number of yeast.

As pointed out earlier, temperature is the most easily changed variable for controlling the fermentation. Glucose and alcohol content vary according to the relationship between the temperature and amylase concentration. Accordingly, in order to use this kind of simulation, it is necessary to prepare inputs by measuring glucose and alcohol concentrations at frequent intervals and to control the fermentation rate based on the relationship between the temperature and the glucose and alcohol concentrations. If that is the case, it may be better and easier to control the fermentation rate relying on the variations of k_1,k_a, Arrhenius type rate relations as presented by Formulas (3) or (4) in simplified forms if necessary, it is all right to introduce corrective terms.

While this paper was being prepared, the Japan Fermentation Engineering Society meeting program (15-17 October 1985) was announced. According to this program, Sugimoto et al. were scheduled to present a paper "Sake-moromi fermentation control using a micro-computer."[12] It is expected that Sugimoto's presentation is most likely to deal with the rate relationships discussed with the last four equations. We regret and feel uncomfortable about having to finish writing this paper without having the privilege of reading Sugimoto's paper. We hope and expect that Sugimoto's work will shed more light on this subject, and we feel very relieved and grateful.

Concluding Remarks

Unlike the vague approach to the sake-moromi fermentation control which has been customary in the brewing industry, we have attempted to achieve complete control of the process by determining rate formulas by a keen analytical approach and using computers. But the theoretical foundation is still weak. From a practical standpoint, we believe we have accomplished our objective.

The more complicated the mathematical equations describing the process, the more explanation can be presented from the theoretical viewpoint. However, in practice we are forced to come up with empirical equations based on the experimental data. As far as simulation goes, it is desirable to minimize the number of variables (variables that can be varied externally and can be used as the control factors) for the control system to be practical. In the case of sake-moromi, the only variable that can be controlled after the feedstock is packed into the reactor is the temperature. Of course, supplementing the enzyme in the middle of the reaction can be an added control factor and it is absolutely necessary to investigate this point.

A special fermentation tank (totally automatic OS plant) equipped with a unique agitation mechanism has been developed for obtaining a homogeneous reaction mixture. We would have liked to deal with this type, but due to the limited space, we reluctantly gave it up. The equipment design should be based on the principle of a simplicity. Since the sake-moromi fermentation is a slow process, we would like to emphasize that it would be well not to give too much thought to sensor installation.

Finally, we express deep gratitude to Dr Kimio Iwano, Brewing Test Laboratories, Department of National Tax, for his contribution of many valuable data and discussions.

FOOTNOTES

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ISSUES IN LSI AUTOMATION, PROTOCOL STANDARDIZATION

Tokyo DENSHI KOGYO GEPPO in Japanese Sep 85 pp 14-20

[Article by Naoshi Sugiyama, chief of CA section, headquarters of system LSI promotion development, NEC Corp.: "Toward LSI Production Automation and Protocol Standardization"]

[Text] 1. Preface

Though not only always predominant in comparison with other industries, the automation of the super LSI factory has continuously made firm progress in the precise control of manufacturing conditions and unmanned application by computer control in order to comply with fine pattern devices, high integration application and short-term manufacturing.

The initial patent for full-scale automation in the LSI factory was the QTAT-related application from TI Corp. in 1969 and IBM Corp. in 1972. The initial automated technology was in the individual automation of cassette to cassette where the semiconductor equipment itself was closely looped, and on to the on-line application with the computer gradually being promoted, progressing to automation of feed-forward, feedback related with manufacturing and maintenance.

Recently, conveying technology has also been satisfactory while automated line consistently synchronizing the flow of products and information is being realized. However, in order to realize the complete unmanned factory, many problems such as clean robot technology, clean transfer technology and fault restoration countermeasures have to be solved. This article will initially touch on the present conditions of automation technology and then next present the standardization trend of hardware and software (communication agreement protocol) essential to the construction of unmanned factories.

2. Automation of LSI Manufacturing

(1) Necessity of factory automation

The Cave [as published] if the LSI chip cost is given by the following formula.

Cave = K x R/W,

R = equipment depreciation cost + construction related expendables (auxiliary material cost) + direct material cost + labor cost + fixed charge

W = wafer injection volume x wafer yield x yield

K = constant

As factory automation aims at minimizing the Cave, various expenditures under R item should be controlled and W item should be increased as much as possible. In the R item, the equipment cost becomes greater along with enlargement of the wafer diameter and fineness of the pattern. The auxiliary material cost and direct material cost are factors for their reduction by rectification of the mask, but they are generally placed toward the increasing direction. The labor cost can be reduced considerably by manpower saving through factory automation and the fixed cost through minimizing the clean area in the factory. For the W item, it is desirable to increase it by improving production efficiency. The wafer yield increases, along with application of the fine patterns and enlargement of the wafer diameter. Precise control of the manufacturing equipment is indispensable to the factory automation technology for fine patternization. The wafer injection volume can be increased by instituting control and controlling the lot flow. The improvement of yield can be increased by introduction of the quality evaluating simulation technology or decrease of work errors by FA application, or decreasing volume of waste by unmanned application.

Although the relation between the chip cost factor and FA application was stated above, the cost of equipment consumption occupies a big ratio of the R item. Figure 1 shows the equipment cost per manufacturing process 2 years ago and at present. The total amount increased 3.5-fold and the ratio of equipment investment in the PR process is extremely large.

The major factor in this is an alternation from the contact method to the miniature project method (stepper). Therefore, full efficient operation of the stepper unit occupying this high equipment cost is one of the points for lowering the chip cost. It is necessary to check the stepper unit each time in the replacement of the reticule to insure that there is no dust. By some format procedure for reticule replacement, time in checking dust can be eliminated and thus actual exposure time can be decreased. Figure 2 shows the relation between the lot injection volume and lot processing time by comparison of optimum operation and poor operation of the stepper, and a remarkable difference of operational efficiency appears along with an increase of the lot injection volume. The FA application is to determine that the lot process procedure approaches as near as possible for optimum operation.

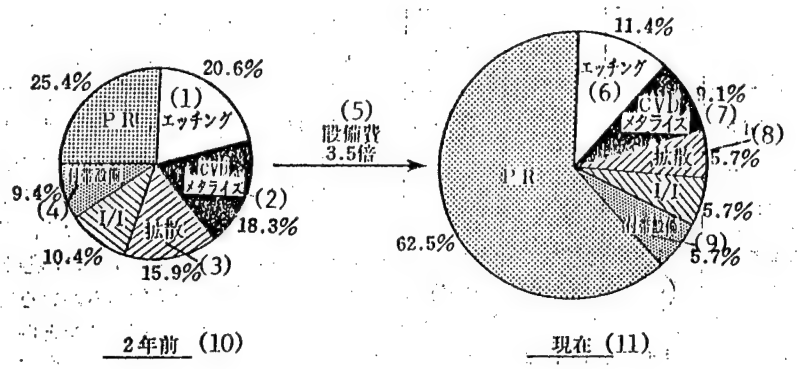

Figure 1. Comparison of the Individual Process Equipment Cost

Key:

1. Etching
2. Metalize (CVD)
3. Diffusion
4. Additional equipment
5. Equipment cost - 3.5-fold
6. Etching
7. Metalize (CVD)
8. Diffusion
9. Additional equipment
10. Two years ago
11. Present

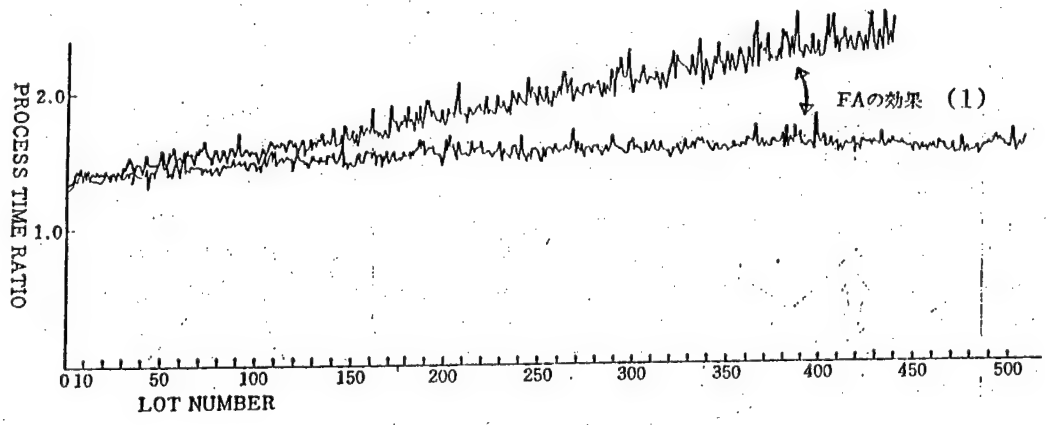

Figure 2. Condition of Stepper Operation (Effect of Control System Application)

Key:

1. Effect of FA

(2) Productivity of Various Production Lines

The range of FA application differs in accordance with the object production line. For example, in the mass production directional line that produces much the same kind of product, such as 64K, 256K DRAM, emphasis is placed on the maximum increase of equipment operation efficiency and cost lowering. In order to maintain the condition in which the equipment has no clearance, usually, the line requires a starter which would prolong the construction period naturally. On the other hand, in the TAT (construction period) directional line that manufactures only such products as the samples, although small in quantity but in urgent need, it is necessary to decrease greatly the injecting volume in the production line giving leeway to the equipment operation. However, TAT may be guaranteed, as the cost increases, problems in industrial operation occur.

Therefore, the combined line capable of following not only TAT directed products but also the mass-produced products in lowering cost can be considered as a type of preferable future production line. Figure 3 shows a comparison of the three types of production line. In order to clarify the difference between the mass production line and the combined line, Figure 4 shows a relationship between the number of the completion lot and TAT.

(3) Various Types of FA Application Technology

1) FA concept

The FA system in the LSI manufacturing process consists of such modules as i) the production plan-schedule plan, ii) product distribution control, iii) precise control, iv) carrier technology, v) technology analysis support, vi) trouble restoration support, and vii) material control.

The i) division is contained generally in the range of production control and is treated in many cases with a distinction from the ii - vii production control. This paragraph describes the FA technology relating to the product distribution control, precise control.

2) Physical distribution control

As stated above, in accordance with the character of the production line, the flow method of products (lot) differs naturally, but the common problems are discussed herewith. The general LSI manufacturing process has the following environmental conditions.

(i) Processing by the same equipment is repeated many times.

(ii) Although it may be the same equipment, (manufacturing procedure steps to manufacture products is ordinarily 200-500 steps), when processing the equipment, installation conditions differ also.

(iii) The equipment for batch treatment (incapable of treating the lot number together) and leaf treatment (treats sheet by sheet) are mixed.

	(1) TAT	(2) 設備稼働率	(3) コスト
(4) 多量生産指向ライン	△	◎	◎
(5) TAT指向ライン	◎	△	△
(6) 併用ライン	○	○	○

Figure 3. Comparison of Various Production Line and Operational Conditions

Key:

1. TAT
2. Ratio of equipment operation
3. Cost
4. Mass production indication line
5. TAT indication line
6. Combined treatment line

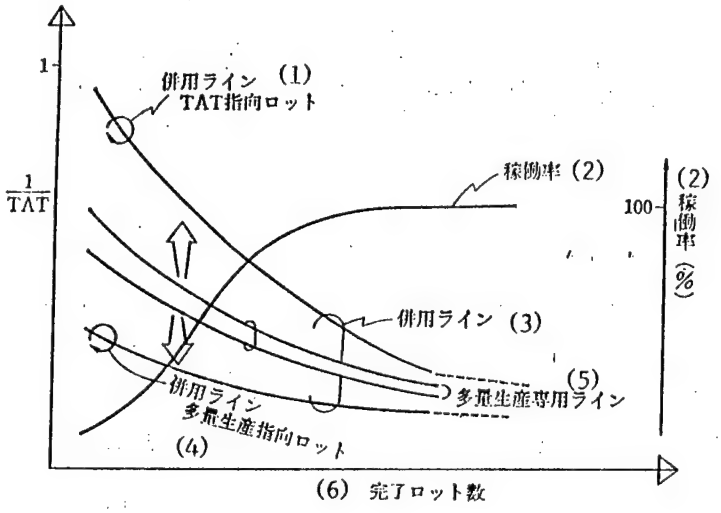

Figure 4. Productivity of Various Production Line--TAT and Production Volume

Key:

1. Combined treatment line TAT indication lot
2. Rate of operation
3. Combined treatment line
4. Combined treatment line mass production indication lot
5. Special line for mass production
6. Number of completed lot

(iv) After completion of the pre-process, the next process should be treated within the prescribed time limit.

(v) The lot is designated with a priority degree. The priority degree differs in accordance with the line characteristics, such as delivery dates delayed due to equipment failures, and the emergency nature of products, etc.

(vi) Performing reconstruction work (restarting from the middle of a procedure) caused by mistakes, etc. in midconstructing process.

(vii) Equipment breakdown ratio cannot be ignored against state-of-the-art process.

(viii) The ratio of equipment operation differs in accordance with the lot order of the equipment. The preparatory time before treatment by the equipment is affected by the lot order. The product distribution control means a lot flow control for maximizing the throughput of production line under the aforesaid environmental conditions.

3) Precision control

The alteration of the manufacturing parameter (temperature treatment, current, etc.) of the manufacturing equipment is considered to affect the record of the final inspection (yield gain, leakage in current, time delay, etc.). It is difficult to clarify the cause-effect sequence relationship between the manufacturing parameter and inspection result for the following reasons:

(i) Due to a variety of manufacturing processes it is difficult to give specifics affecting the evaluation on the final products in the especially processed work condition.

(ii) There should be numerous indexes for evaluation of products. Therefore, a special comparison of manufacturing parameter and evaluation index cannot be made.

As the direct analysis is difficult, a statistical technique is applied. Figure 6 shows a simulation concept and aims at analyzing the relationship between the inspection data and the manufacturing parameter statistically, based on the measured value.

3. Standardization Technology for FA Application

(1) Background of standardization promotion

In the super LSI factory, FA application is promoted for complete unmanned application. There is the great merit that not only does unmanned application make rationalization possible, but also with the minimizing of crowds, the source of litter, can bring about dust-free conditions contributing to increased yield.

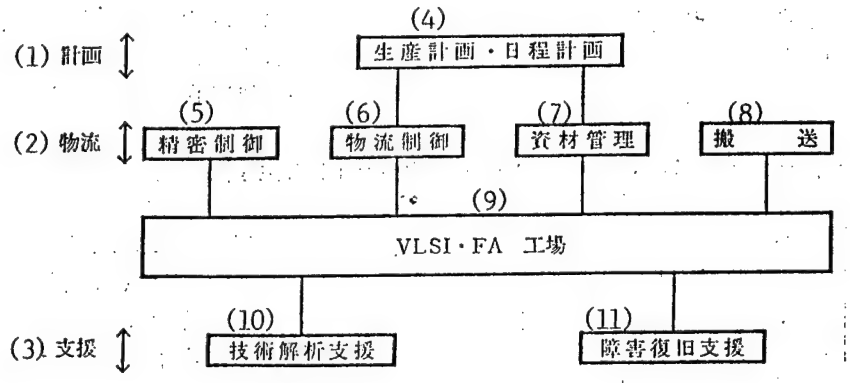

Figure 5. FA System (Production Control)

Key:

1. Plan
2. Product flow
3. Support
4. Production plan-schedule plan
5. Precise control
6. Control of product flow
7. Control of materials
8. Transfer
9. VLSI-FA factory
10. Technology analysis support
11. Fault restoration support

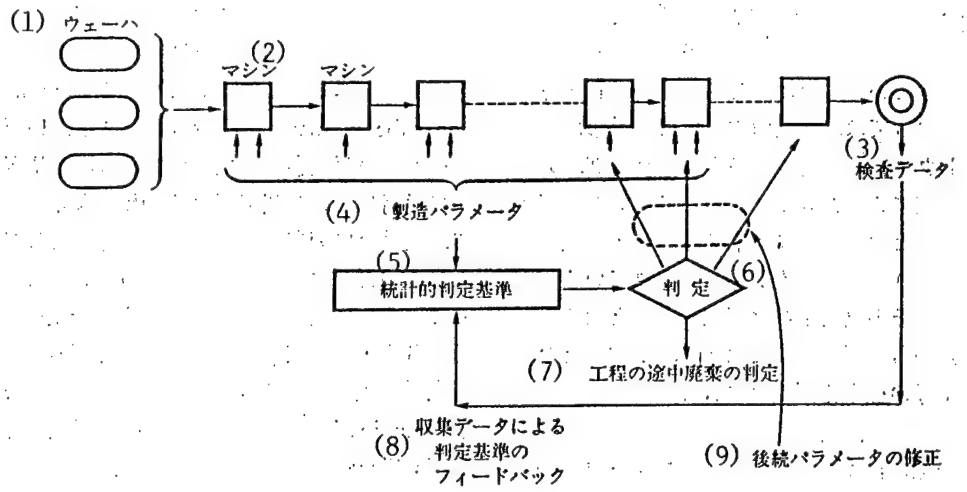

Figure 6. Simulation of Quality Estimation (Unification of Quality, Improvement of Yield)

Key:

1. Wafer
2. Machine
3. Inspection data
4. Manufacturing Parameter
5. Statistics judgment standard
6. Judgment
7. Judged for abolishment in midprocessing
8. Feedback of judgment standard by collection data
9. Rectification of following parameter

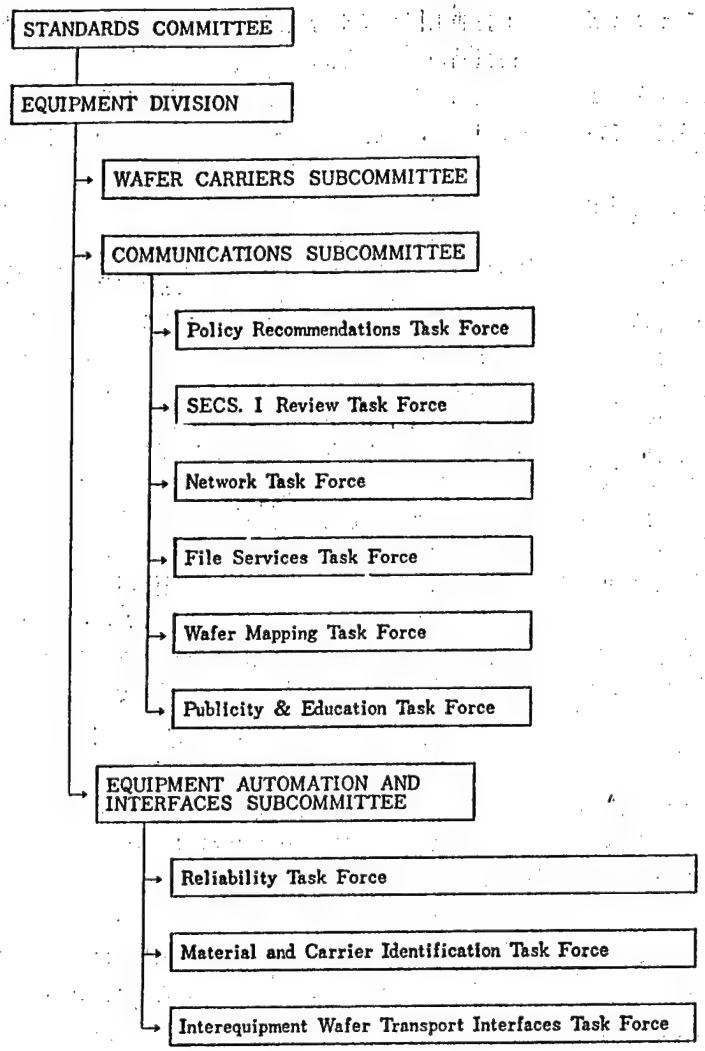

Figure 7. Diagram of Committee Organization

The FA factors that accelerate the realization of an unmanned applied factory are:

(i) To standardize the communication procedure and agreement (protocol) between the host computer and production equipment.

(ii) To standardize the method for taking the carrier out from and/or into (loader, unloader) the production equipment.

As the makers of production equipment have conventionally determined the protocol method of (i) above, loader, unloader method of (ii) above, as mentioned, in order to promote FA in the LSI factory development of the software along with the communication procedures of the individual equipment and that of the robot-handling technology suitable for the loader and unloader method of the individual equipment are necessary. When considering the year after year mechanism improvements of the production equipment and repetitious equipment alterations, the number of their developments are gigantic. From the aforementioned background, in the United States, the aforementioned (i), (ii) standardizations, centering on SEMI, is being studied.

(2) Standardization committee

The SEMI standardization committee includes a communication subcommittee for promoting the standardization of the protocol and an Equipment Automation and Interface Subcommittee for promoting the standardization of the equipment interface. The respective committee as shown in Figure 7 is divided into the task force for deliberation on various themes. The joint committee conducts meetings four times a year. (January--West Coast Area, May--Semicon West, September--Semicon East, November--Southwest Area) and anyone, including non-committee members, may freely.

In Japan the No 12 special committee is established within the silicon special committee (Agriculture Industrial University--Professor Tarui) sponsored by the Electronic Association discussed the standardization of communication procedures. Its members consist of the six leading makers of computers and in addition, a few equipment makers. The regular meeting is held on an average of every 2 months; however, its main discussion is on the contents of standardized documents in the United States (SECS: The SEMI Equipment Communication Standard) and any questions or items for request are Japan's opinion reflected in the standardization of SECS. In December 1984 the first Japanese-U.S. joint committee was held in Japan and the opinions of the Japanese side were stated. In May 1985 the authors attended the communication subcommittee meeting in the United States to explain the 15 request items of the Japanese side, as well as the activity status of the promotion for standardization.

The requesting items became a draft and it was distributed to every committee member and whether it was adopted as an SECS standard was determined by vote. The special committee held a symposium of super LSI-FA technology in order to promote SECS.

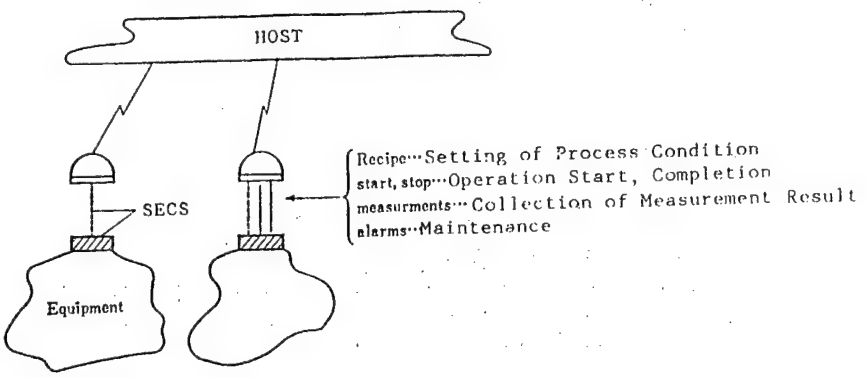

Figure 8. Transfer of Data via SECS

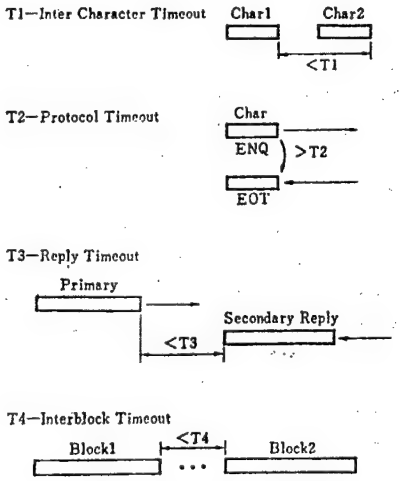

Figure 9. TIMEOUTS

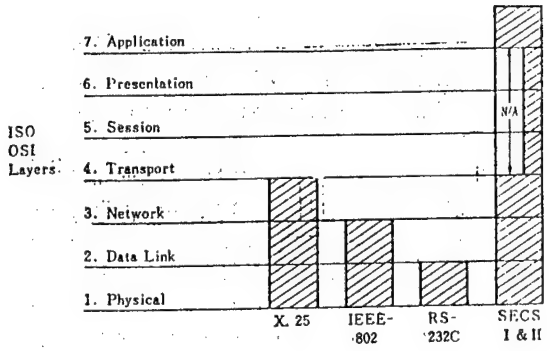

Figure 10. Article Range of SECS (ISO Comparison)

Starting with an orientation by Professor Tarui, Agricultural Industry University, lectures on SECS by Chris Clare, a member of the Communication Subcommittee, and for the SECS executing side regarding the FA factory by Klaus Schuegraph (Tyrun) Co., Ltd., followed, and finally a panel discussion "FA Role of the Super LSI Factory" was held by the six computer companies. The symposium had initially expected to have about 100 participants, but found that there were 300, and the meeting place was quickly changed. The discussions were lively and the importance of FA application and SECS were recognized again.

(3) SECS Agreement

The SECS agreement was based on those used by HP Corp. while the topic of standardization was brought up in SEMI 1979. In 1980, the SECS-1 agreement and in 1982 the SECS-2 agreement were reached. Thereafter, the message expansion and study on network countermeasures, etc. progressed. At present, as a "moving document" the function has been improved. Figure 8 shows the content of ruling on data transfer through SECS, such as receipt (establishing condition of process), the start-completion of operation, collection of the measurement result and maintenance information, etc. It also includes the limitation on time out (Figure 9) and multiblock transfer. Figure 10 shows a comparison of the scope of SECS rulings with other communication procedures. Its feature is that it prescribes up to the application layer in the ISO agreement.

(4) Standardization of hardware

The unification of the load-unload mechanism of wafer carrier from the production equipment enables the transferred carrier equipment to be installed-detached uniformly by robot handling, even if the production equipment is different. The SMIF technology (the Standard Mechanical Inter Face) was suggested by the HP Corp. as a means of standardization. Figure 11 [Figure 11 not included in original] illustrates the SMIF mechanism. The wafer is stored in a case called the SMIF box where a cleanliness degree of class 10 is maintained, and it is attached-detached into the production equipment by the elevator mechanism and manipulator. The SMIF technology is utilized at present only by U.S. GCA Corp. and a few other corporations, but as it had been discussed as a theme study in the aforementioned Equipment Automation and Interfaces Subcommittee. The SMIF specifications will be improved in the future, and utilized by equipment makers. Venture businesses commercializing SMIF have already been appearing

4. Conclusion

The FA technology and standardization movement in the super LSI factory has been outlined. The standardization of software (protocol) has been discussed by the Electronic Association and as a result the importance of SECS has emerged among domestic IC makers and equipment makers. In the future, the individual corporations should make efforts for standardization, and although the problem relating to know-how in the factory is partially included, there are many points such as the limitation in the scope for the bylaws of standardization and its definition.

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FISCAL 1984 POWER DISTRIBUTION RECORD

Tokyo DENKI TO GASU in Japanese Jul 85 pp 15-17

[Article by Jinpei Murooka, Developmental Section: "Actual Generation and Supply of Electricity in 1984"]

[Text] The actual performance of 1984 electricity generation and supply has been compiled and the outline is presented.

I. Demand

Due to an increase in airconditioning related demand caused by another summer of high temperature following last year, in addition to the demand for industrial use which indicated a smooth growth based on business recovery, the total power generation/supply of the nine electrical power companies in fiscal 1984 rose to 552.4 billion kwh (104.7 percent against the previous year, 103 percent against the plan). (Tables 1 and 2)

On the other hand, following the increased demand during the summer, the total maximum generation of the nine companies surpassed the past record for the first time, the 100 million kw level, for a maximum 3-day average (at transmission terminal) and reached 136.9 million kw, a new record this year for each company (Table 3).

Furthermore, the Hokkaido Electrical Power Company, Inc., achieved a winter peak of 3.01 million kw in December the same year for a continual surpassing of the record.

II. Supply

As to hydraulic power generation, the nationwide water-shortage trend continued throughout the year which was aggravated by the early ending of the rainy season with no typhoon hitting the island and additionally, the water level became abnormally low following fiscal 1983 making the total rates of water release by the nine companies at 92.5 percent for the first half of the fiscal year (seventh lowest level), 77.2 percent for the second half (lowest), and 86.1 percent for the annual total.

As a result, total power generation of the nine companies was at 52.7 billion, remaining 86.7 percent against the previous year and 86.7 percent against the plan.

Table 1. Amount of Generated Power and Supply (total of nine companies)

	Power generated/ supplied (100 million kwh)	Ratio against previous year (percent)	Compared with plan (percent)
First half	2,775	106.6	103.1
Second half	2,749	102.8	102.8
Fiscal year total	5,524	104.7	103.0

Table 2. Power Generation/Supply by Respective Companies

	Power generated/ supplied (100 million kwh)	Ratio against previous year (percent)	Compared with plan (percent)
Hokkaido	195	101.8	98.7
Tohoku	470	105.7	105.2
Tokyo	1,741	105.8	104.1
Chubu	813	105.2	103.3
Hokuriki	189	104.3	102.5
Kansai	1,040	104.0	102.2
Chugoku	394	103.5	101.6
Shikoku	198	103.2	102.7
Kyushu	481	103.6	100.8
Total of nine companies	5,524	104.7	103.0
Okinawa	39	102.4	102.9

Note: Total number does not agree as the numbers are rounded off.

Table 3. Maximum Power Generated (3-day average at transmission terminal)

	Maximum power output (10^3 kw)	Ratio against previous year (percent)	Compared with plan (percent)	Supply surplus ratio (percent)	Annual liability percentage
Hokkaido	2,898	102.3	98.3	15.7	74.0
Tohoku	7,640	109.3	106.3	8.6	68.0
Tokyo	33,950	104.8	103.3	7.2	56.4
Chubu	15,595	109.6	105.8	9.1	53.3
Hokuriku	3,324	106.0	102.3	9.2	63.8
Kansai	20,496	102.7	98.8	11.5	55.5
Chugoku	7,134	104.5	106.0	12.4	60.6
Shikoku	3,393	100.1	103.8	17.2	63.0
Kyushu	9,256	101.3	100.7	13.8	57.1
Total of nine companies	103,686	104.9	102.7	10.0	58.5
Okinawa	750	105.5	102.5	18.1	55.9

Moreover, this winter's snowfall was slightly less than the average year nationwide with the average of the 14 areas where snow piled up the deepest (1 March) being 94 percent against the average year.

As for atomic power generation, in addition to the already installed units which were operating smoothly, Onagawa No 1 unit (1 June), Takahama No 3 unit (17 January) and Kawauchi No 1 unit (4 July had begun operation on a business basis, while Fukushima Second No 3 unit (initial parallel operation 14 December) and Kashiwazaki/Kariwa No 1 unit (initial parallel operation 13 February) smoothly started operations on a trial basis; thereby the generated power, including that by Japan Atomic Power Generation, showed a major increase to a record 133.2 billion kwh, 117.8 percent against the previous year and 115 percent against the plan. Facility usage ratio was 73.9 percent, also an increase from the previous year.

As to thermal power generation, the total of the nine companies was 304.1 billion kwh, 104.6 percent against the previous year and 101.5 percent against the plan (Tables 4 and 5).

Table 4. Inundation Ratio and Nuclear Facility Usage Ratio

	Flooding ratio (percent)			Nuclear facility usage ratio (percent)
	First half	Last half	Total for fiscal year	
Hokkaido	75.3	71.3	74.1	--
Tohoku	100.0	75.2	88.7	98.9
Tokyo	92.7	76.5	86.0	71.2
Chubu	82.5	73.1	78.6	70.6
Hokuriku	99.4	80.9	92.0	--
Kansai	97.3	80.0	90.3	72.6
Chugoku	88.2	78.1	83.5	77.8
Shikoku	94.0	72.6	85.2	84.1
Kyushu	89.2	84.6	87.3	83.1
Total of 9 companies	92.5	77.2	86.1	74.5
Japan Atomic Power Corp.	--	--	--	68.2
Grand total	--	--	--	73.9

Table 5. Amount of Electricity Generated/Supplied by Respective Power Sources (total of nine companies

(Unit: 100 million kwh, percent)

		Fiscal year 1984				(Reference)
		Actual	Ratio with previous year	Ratio with plan	Composite ratio	Fiscal 1983 composite ratio
Electrical power companies	Hydraulic power	527	86.7	86.7	9.5	11.5
	Thermal power	3,041	104.6	101.5	55.1	55.1
	Atomic power	1,235	119.9	115.4	22.4	19.5
Received from other companies	Hydraulic power	179	86.8	84.7	3.2	3.9
	Thermal power	483	105.8	106.7	8.7	8.7
	Atomic power	102	95.1	114.9	1.9	2.0
	(Electrical power source development--listed again)	(299)	(94.5)	(97.9)	(5.4)	(6.0)
Power for pumping water		▲44	112.1	71.4	▲0.8	▲0.7
Total generated/supplied		5,524	104.7	103.0	100.0	100.0
Atomic power (listed again) (transmission terminal)	The nine electric power companies	1,235	119.9	115.4	--	--
	Japan Atomic Power	97	95.7	110.4	--	--
	Total	1,332	117.8	115.0	--	--

Note: Total does not agree because of rounding of numbers.

III. Electrical Power Distribution

(1) Nationwide Distribution

Reflecting the stable supply/demand of the respective companies, the distribution adjustment of supply/demand was small--3.75 million kwh for the fiscal year total, 18.4 percent against the previous year.

The economical distribution hit a new record of 1,017,670,000 kwh for the fiscal year total, over the past year's maximum by 167.3 million kwh. Contributing to this were the efforts of respective companies in strengthening mutual cooperation for more precise and efficient operations and supply of electricity in order to cope with changes in the supply/demand structure as a result of an increasing fluctuations trend of the maximum generation due to

weather conditions, the high rate of operation of atomic power generation and the abnormal water shortage.

(2) Two-Company Accommodation

The two-company accommodation resulted in 79.4 percent against the previous year owing to the reduction in the affiliated use of power and the drop in the specified supply. (Tables 6 and 7)

Table 6. Actual Performance of Accommodation

(Unit: kwh, percent)

Type of power accommodation		Fiscal 1984	Fiscal 1983	Previous year ratio
Nationwide accommodation	Power accommodation for supply/demand adjustment	3,750,000	20,430,000	18.4
	Power accommodation for economy	1,017,670,000	910,940,000	111.7
	Power accommodation through mutual adjustment	433,930,000	561,810,000	77.2
	Total	1,455,350,000	1,493,180,000	97.5
Accommodation between two electrical power companies	Specified accommodation	4,249,980,000	(857,100,000) 5,125,520,000	
	Power for affiliation operation	8,663,700,000	10,531,340,000 (766,650,000)	82.9
	Power for affiliation accommodation	523,080,000	1,275,350,000	41.0
	Total	13,436,700,000	16,932,210,000	79.4
Grand total accommodation		14,892,110,000	18,425,390,000	80.8

Notes: 1. Number in parentheses for specified accommodation represents component number in reference to the development adjustment accommodation relative to No 2 unit of Higashi Niigata.
2. Number in parentheses for affiliation accommodation represents component number in reference to the trial-operation-related accommodation for Nakoso No 8 and No 9 units.

Table 7. Record of Actual Supply of Economy Accommodation Power

(Unit: kwh)

Precedence order	Fiscal year	Total economy accommodation power	Breakdown		
			Economy A power	Economy B power	Economy C power
1	1984	1,017,670,000	963,440,000	54,230,000	0
2	1983	910,940,000	851,360,000	30,280,000	29,300,000
3	1982	863,980,000	857,380,000	4,100,000	2,500,000

IV. Outline of Facilities

During fiscal 1984, power generation facilities of 5.16 million kw capacity were newly built for year-end facilities of a 143.21 million kw capacity. (Table 8)

Table 8. Status of New Construction—Abolition of Power Generation Facilities (including facilities for receiving power from other companies)

(Unit: 10,000 kw, percent)

	Fiscal 1984					(Reference) Fiscal 1983	
	New construction	Conversion	Abolition	Facilities at end of year	Composite ratio	Facilities at end of year	Composite ratio
Hydraulic power	45	--	2	3,270	23	3,227	23
Thermal power							
Nonpetroleum related	55	450	13	4,070	29	3,578	26
Petroleum related	188	Δ450	78	4,925	34	5,265	38
Total	243	--	91	8,995	63	8,843	64
Atomic power	228	--	0	2,056	14	1,828	13
Grand total	516	--	93	14,321	100	13,898	100

(1) The hydraulic power was 450,000 kw with 34 units--the No 2 unit of Shikoku in Hongawa (300,000 kw pumping water).

(2) The thermal power was 2.43 million kw with eight units--the No 3 unit of the third system of Tohoku in Hagashi Niigata (545,000 kw) and Nos 1-3 units of Kansai in Gobou (600,000 kw x 3).

(3) The atomic power was 2.28 million kw with three units--No 1 unit of Tohoku in Onagawa (524,000 kw), the No 3 unit of Kansai in Takahama (870,000 kw), and the No 1 unit of Kyushu in Kawauchi (890,000 kw).

V. Pertaining to Okinawa

The fiscal 1984 actual performance by Okinawa Electrical Power Company, Inc., resulted in approximately 3.9 billion kwh of annual generation (102.4 percent against the previous year, 102.9 percent against the plan); and approximately 750 kw of the maximum 3-day average generation (105.5 percent against the previous year; 102.5 percent against the plan).

The capacity was approximately 980,000 kw for the fiscal year-end facilities.

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CSO: 4306/5036

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